ASSESSMENT OF INSULIN RESISTANCE IN OFFSPRING OF DIABETIC AND NON DIABETIC PARENTS

DISSERTATION SUBMITTED FOR

M.D., BRANCH-V (PHYSIOLOGY)

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THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY,

CHENNAI, TAMILNADU.

MADURAI MEDICAL COLLEGE, MADURAI

CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled **"ASSESSMENT OF INSULIN RESISTANCE IN OFFSPRING OF DIABETIC AND NON DIABETIC PARENTS''** submitted by **Dr.S.KANNAN** to the Faculty of Physiology, The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the reward of M.D. Degree in Physiology is a bonafide work carried out by him during the period 2016-2019.

Place: Madurai
Date:

Prof.Dr.D. MARUTHUPANDIAN
M.S., F.I.C.S., F.A.I.S., FAC
Dean,
Madurai Medical College &
Govt. Rajaji Hospital, Madurai.

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This is to certify that the dissertation titled **"ASSESSMENT OF INSULIN RESISTANCE IN OFFSPRING OF DIABETIC AND NON DIABETIC PARENTS''** is a bonafide record work done by **DR.S.KANNAN,** under my direct supervision and guidance, submitted to The Tamilnadu Dr. M. G. R. Medical University in partial fulfillment of University regulation for **M.D., Branch-V (Physiology).**

Dr.P.S.L.Saravanan, M.D.,
The Director (i/c) and Professor,
Institute of Physiology,
Madurai Medical College,
Madurai.

DECLARATION

I **DR.S.KANNAN,** solemnly declare that the dissertation titled ‘‘**ASSESSMENT OF INSULIN RESISTANCE IN OFFSPRING OF DIABETIC AND NON DIABETIC PARENTS ’’** has been prepared by me. I also declare that this work was not submitted by me or any other, for any award, degree, diploma to any other University board either in India or abroad. This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of **M.D degree Branch-V (Physiology)** to be held in **May-2019.**

Place: Madurai **Dr.S.KANNAN**

Date:

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INDEX

INTRODUCTION

INTRODUCTION

Diabetes mellitus is a major pressing public health concern associated with a rapidly growing socioeconomic burden. Globally 80% of lower and middle income countries are suffering from it. The WORLD HEALTH ORGANIZATION has estimated that in 2017 India had 72 million people living with diabetes with the prevalence rate of 8.8%. The number of cases is expected to increase to 101.2 million by 2030.

Among this epidemic of diabetes the prevalence of type 2 diabetes mellitus or NIIDM (Non insulin dependent diabetes mellitus) due to insulin resistance accounts for over 85% of diabetes worldwide, and this incidence depends on different genetic variation, different environmental, dietary habits and various geographic factors in population that has allowed the problem to grow at frightening rate during the past few decades. Genetic factors remains the main cause of Diabetes mellitus throughout the world, sedentary lifestyle and obesity remains the other causes.

Pathological and etiological factors for Diabetes mellitus have been extensively studied and it is now considered one amongst of the major diseases with multifactorial genetic as well as environmental pattern of inheritance based on familial clustering.

Family history is an important component of genetic background for development of diabetes mellitus. Transmission of genes to the offspring is a significant risk factor for diabetes in the future. A greater probability to acquire type 2 diabetes mellitus was seen among offspring of

diabetic parents compared to those of non-diabetic parents in Indian population. Offspring of diabetic parents showed an increased risk of diabetes mellitus in western world with an age range of 35-45 year old.

People who develop type 2 diabetes mellitus usually passes through stages of **insulin resistance** initially, which is characterized by a reduced ability of insulin to stimulate glucose uptake in skeletal muscle, it is also part of a larger constellation of several symptoms called the metabolic syndrome. This stage of insulin resistance often go undiagnosed and unnoticed.

Insulin resistance is a pathological condition in which cells normally fail to respond to insulin hormone.

Insulin resistance is syndrome resulting from reduced insulin activity and is a metabolic defect observed as an early event of genetic origin and it is a primary cause of the subsequent development of type 2 diabetes mellitus. Insulin resistance may be traced number of years before onset of diabetes mellitus.

In 1985, Matthews *et al.*. First described under the name HOMA-IR (**Homeostatic Model Assessment Of Insulin Resistance**) is a method used to quantify insulin resistance which is simpler, cheaper, less labor-intensive, less time consuming and more acceptable to young people and more practical method for application in large epidemiologic studies.

HOMA-IR is an estimate of insulin resistance derived from fasting glucose and fasting insulin levels, with higher levels representing greater degrees of insulin resistance.

Diabetes can cause most extensive damage if left untreated. Diabetes may cause damage to vital organs of the body such as heart, kidneys, eyes and brain. Recent studies have shown that type 2 diabetes can be prevented by changes in lifestyle modifications of high risk subjects. ELLIOT JOSLIN in 1920 identified exercise, along with dietary management had improved the insulin sensitivity.

Early screening for insulin resistance in young age, at least in offspring of diabetic parents becomes necessary so that prompt lifestyle modifications will help to delay the onset of Type 2 Diabetes mellitus. Hence we have undertaken a study to screen insulin resistance in offspring of diabetic parents by (HOMA-IR)Homeostatic Model Assessment Of Insulin Resistance.

AIM AND OBJECTIVES

AIMS AND OBJECTIVES

- To determine the levels of serum fasting glucose in offspring of Single Diabetic Parent (SDP) group, Both Diabetic Parents (BDP) group and Non Diabetic Parents (NDP) group.
- To determine the levels of serum fasting insulin in offspring of Single Diabetic Parent (SDP) group, Both Diabetic Parents (BDP) group and Non Diabetic Parents (NDP) group.
- To assess insulin resistance by Homeostatic Model Assessment of Insulin resistance(HOMA-IR) in all subjects of above mentioned groups.
- To compare and analyze Insulin resistance between these groups.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ISLETS OF LANGERHANS - PANCREAS

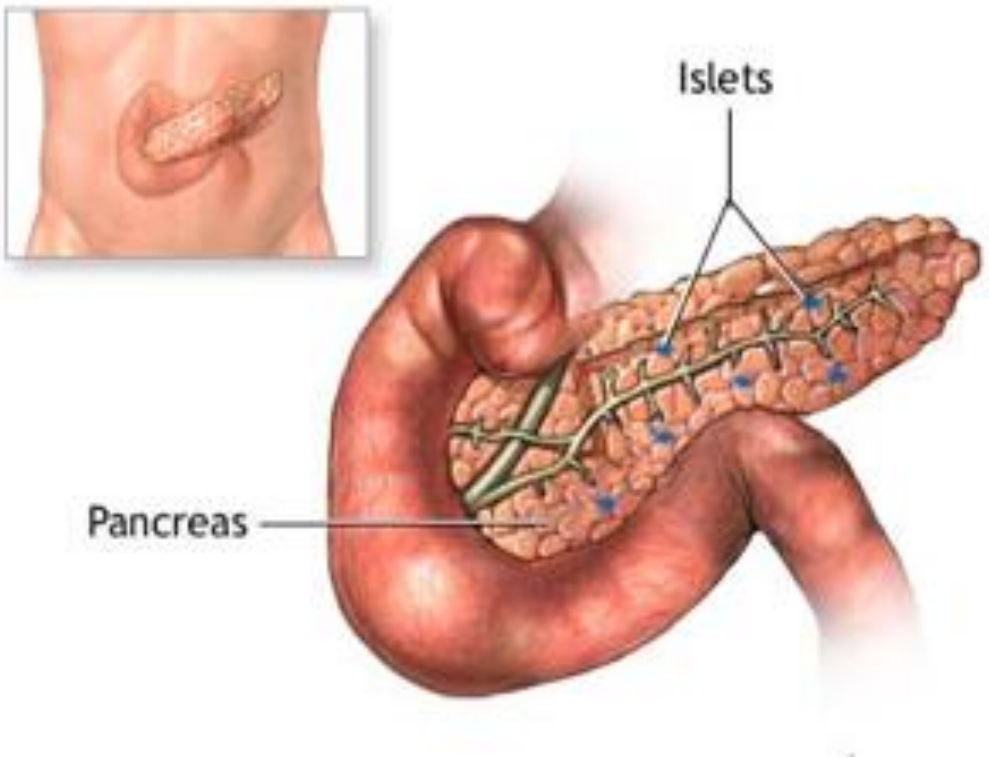
Historical Aspects:

The presence of epithelial tissue in the pancreas is different from the alveoli and ducts was first described as the 'Islets of Langerhans' by great scientists **Langerhans 1869**,**Diamare 1889, and Laguesse 1893** were probably the first persons to suggest that the islet tissue is concerned with the production of an internal secretion which controls carbohydrate metabolism. Then **Schulze 1900, and Ssobolew 1902** found that when they completely blocked the pancreatic duct with paraffin, the resultant sclerosis will led to the destruction of acinar tissues but left the islets unimpaired. **Warthin 1922** has given an very excellent historical account of the discoveries which established well the endocrine function of the islet tissue.

Anatomy of Endocrine Pancreas:

The endocrine pancreas consists of islets of Langerhans, embedded in the exocrine pancreatic tissue. The human pancreas contains roughly 1-2 million islets, usually most numerous in the tail part. An islet is a mass of several polyhedral shape cells each in close proximity to fenestrated end capillaries and a rich autonomic innervation.

PANCREAS



There are three main types of cells designated alpha cells, beta cells and delta cells which secrete glucagon, insulin and somatostatin respectively, **Bjorkman et al 1966**. Alpha cells are concentrated at the periphery of islets of Langerhans and beta cells more centrally located. A minor cell type of cell, the F cell secretes pancreatic polypeptide (PP).

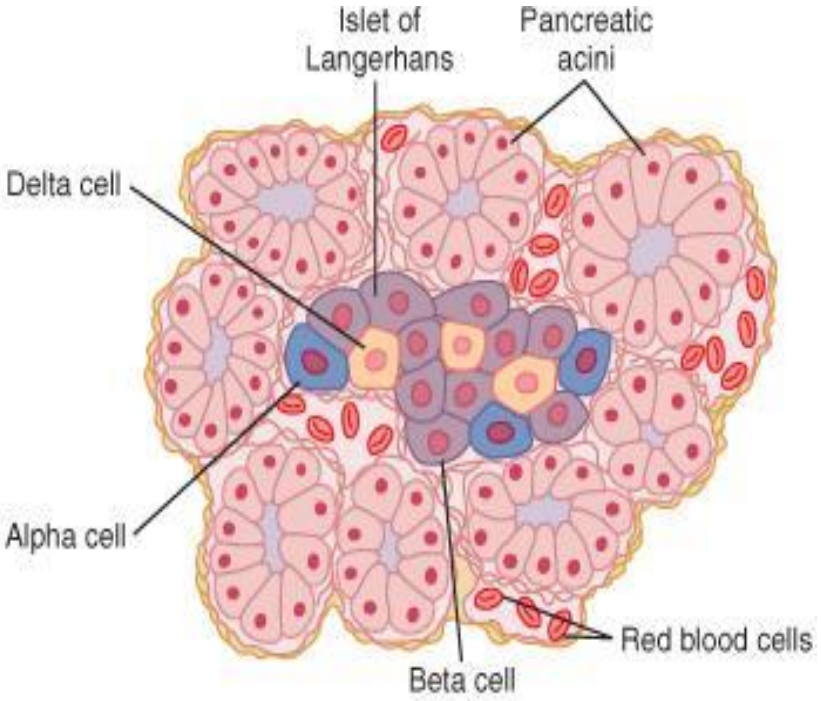
Development:

The endocrine pancreatic cells of islets arise from a common endodermal ancestors region in the pancreatic ducts **Brock et al 1969**. The islets of Langerhans are identifiable by the fourth week of intrauterine life and are capable of hormone secretion by the tenth week **Bonner –Wier S.**

Blood supply:

The islets are exceedingly very well vascularized; they receive only 10% of the pancreatic blood supply. Small arterioles enter the central core of the islet and breakup into many capillaries. These come together into the venules, which then carry the blood to the mantle of the islets of langerhans. This portal arrangement allows higher concentrations of insulin from the beta cell core region to bathe the alpha cells, Delta cells and PP cells of the respective mantle region. Such a complex vascular pattern suggests local paracrine regulation.

ISLETS OF LANGERHANS

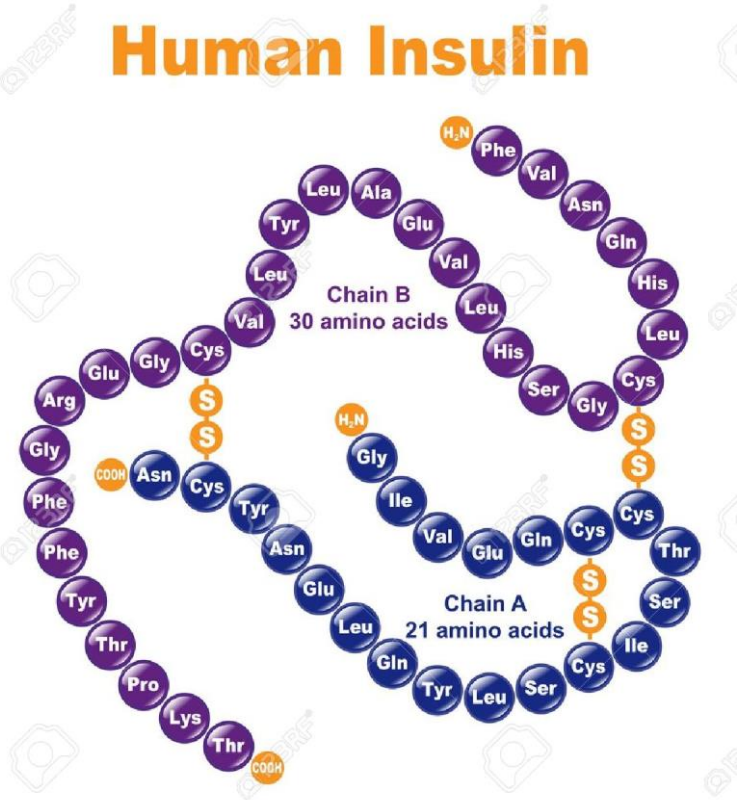


Innervation :

The islets of langerhans are innervated by parasympathetic, sympathetic and peptidergic nerves. Parasympathetic ganglia situated in the connective tissue between the lobules and form neuroinsular complexes.

Three types of nerve terminals are seen in islets of langerhans. Cholinergic terminals mostly have agranular vesicles with a diameter of 30-50nm, adrenergic nerve terminals have dense cored vesicles with the same diameter of 30-50nm and a third uncharacterized type have highly densed cored vesicles with a large diameter of 60-200 nm **Smith and Porte 1976.**

STRUCTURE OF INSULIN



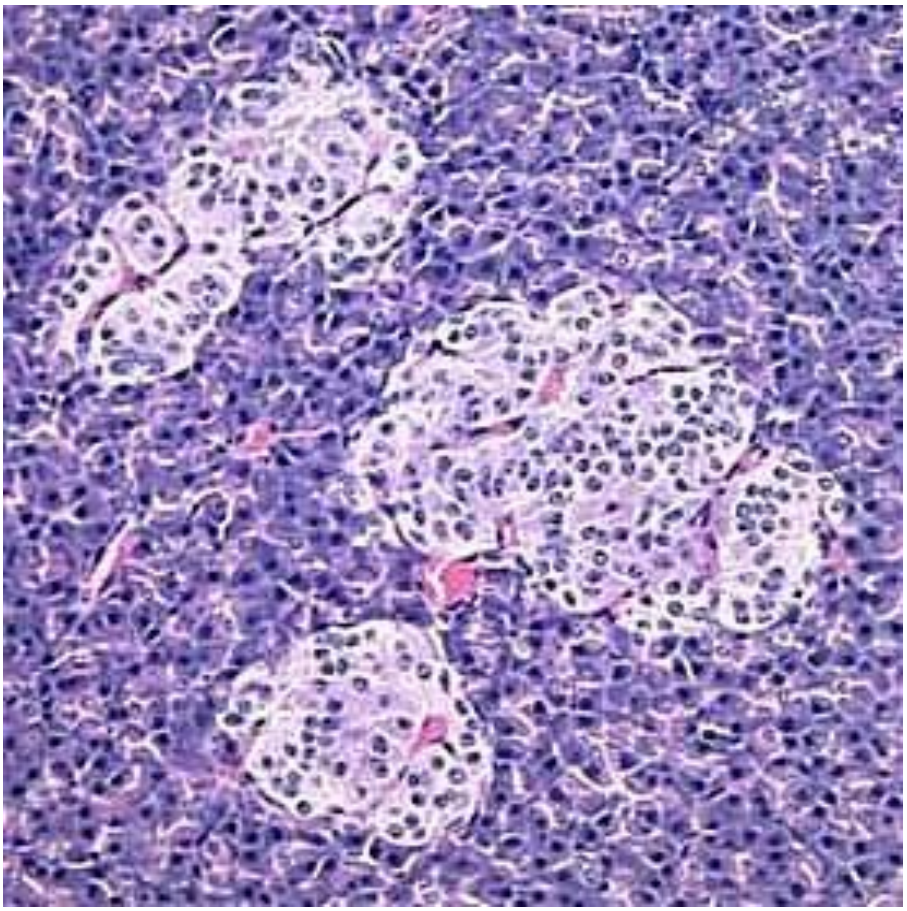
INSULIN

HISTORICAL ASPECTS:

The major credit for the preparation of a pancreatic extract which is capable of lowering the blood sugar level belongs to **Dr. Frederick Banting and Dr.Charles Best**. 1n 1921, they discovered insulin hormone by tying a string around the pancreatic ducts of several dogs. When they examined these pancreatic tissue of the dogs several weeks later, all of these digestive pancreatic cells were gone leaving behind only thousands of pancreatic islets. Then they used acid ethanol to extract from these tissue, an islet cell factor which had potent hypoglycemic activity and further named it as 'insulin'. Much earlier, **deMeyer in 1909**, and **Sharpey – Schaffer in 1916** proposed the term 'insulin' to denote the internal secretory products of the islet tissue of pancreas, but further it was **Banting and Best**, proved this association in 1921.

Insulin was one of the first proteins proved to have hormonal action, the first protein was crystallized **Abel, 1926**, the first protein that was sequenced **Sanger et al, 1955**, the first protein synthesized chemically **Du et al, Zahn, Icatsoyanis, Ca 1964**, the first protein that shown to be synthesized as a larger precursor molecule by **Steiner et al 1967** and the first protein prepared for the commercial use by recombinant technology. Then the three

MICROSCOPIC STRUCTURE OF ISLETS OF LANGERHANS OF PANCREAS



dimensional structure of insulin hormone was revealed by **Dorothy Hodgkin in1969**.

Structure:

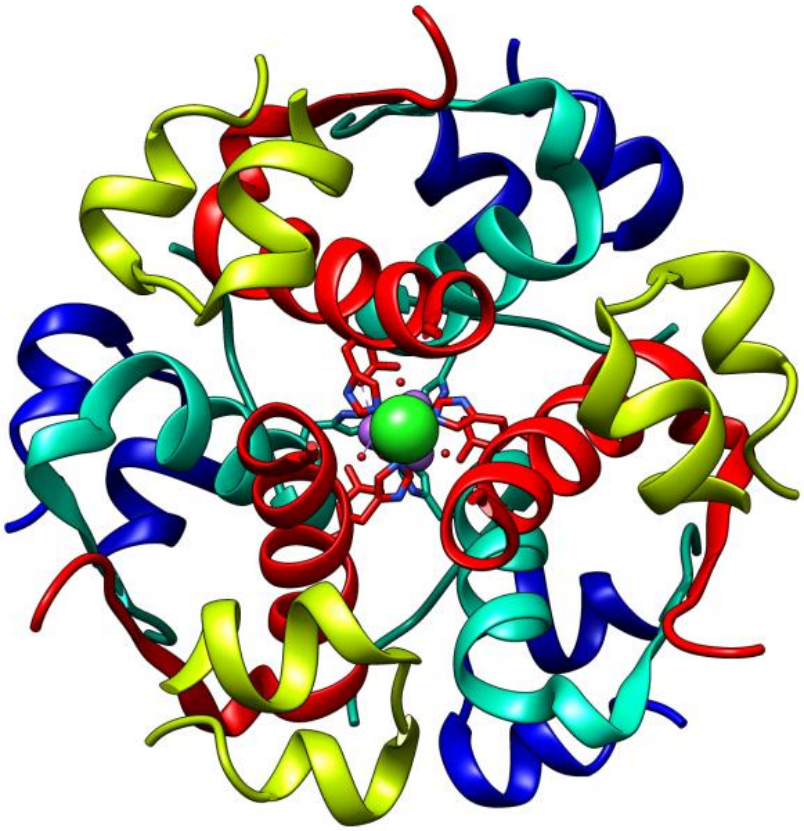
Proinsulin is a protein polypeptide consisting of a chain of around 86 amino acid residues, according to species. **Sanger his co-workers** proposed Insulin and proinsulin can also occur as monomers, dimmers or even hexamers. Beta cell granules contain hexamers with Zinc, but the biologically active form of insulin is the monomer, with molecular weight of about 9000.

Removal of the connecting peptide (c-peptide) from proinsulin produces insulin. Insulin hormone is a heterodimeric structured polypeptide consisting of two chains of amino acids, A and B chains, linked by two disulfide inter chain bridges that connect A7 to B7 and A20 to B19. Another third intra chain disulfide bridge connects between residues 6 and 11 of A chain. The location of these disulfide bridges is common and the A chain has 21 amino acids and B chain has 30 amino acids **Nicol D.SH and L.F.Smith 1960.**

BIOSYNTHESIS AND SECRETION OF INSULIN:

The tremendous work of **Grante et al in 1970** has shown that the mechanisms involved in the biosynthesis of hormone insulin under physiological conditions are much complex. **Macleod in 1922**

INSULIN STRUCTURE



first observed that hormone insulin is produced and stored in the pancreatic islets of langerhans.

Proinsulin is synthesized by the ribosomes on rough endoplasmic reticulum, and enzymatic removal of the peptide segment leads to disulfide bond formation, and the folding occur in cisternae of this organelle. This proinsulin molecule is transported to Golgi apparatus, then proteolysis and packaging into secretory granules occurs **Jamieson et al, 1971**. C-peptides are present in equimolar concentrations within these granules and these molecules do not form crystalline structure. While appropriate stimulation, the mature granules fuse with plasma membrane and discharge its contents into the extracellular fluid **Lacy, 1961.**

The insulin gene is located on the short arm of chromosome 11 and it has two introns and three axons.

REGULATION OF INSULIN SECRETION:

The normal concentration of the fasting insulin measured by radioimmunoassay in humans is 3-11 μU/ml (18-48 pmol/L). The amount of hormone insulin secreted in the basal state is 1U/h, with a tenfold increase following ingestion of food and the average amount secreted per day in humans is about 40U (287 n mol).

Insulin secretion is regulated by

i) Substrate stimulation

ii) Hormonal regulation

iii) Neural regulation

i) Substrate stimulation

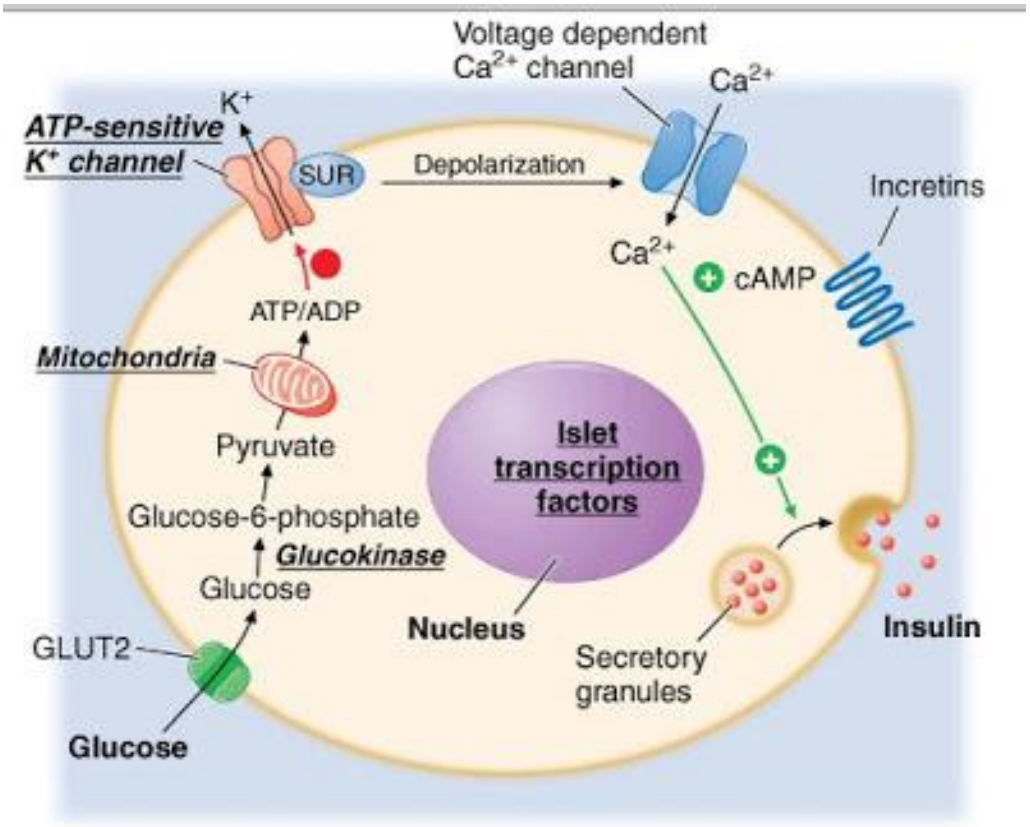
The most important factor in the control of insulin secretion is substrate stimulation. Carbohydrates and proteins are of prime importance and lipids have no significant effects. An increase in blood glucose concentration is the important physiologic regulator of secretion of insulin **Permutt, MA and D.M Kipins 1970.**

The threshold concentration for insulin secretion is the fasting plasma glucose level (80-100 mg/dl) and the maximal insulin secretion is obtained when the glucose is biphasic and there is a rapid but short lived rise in secretion followed by more slowly developing and prolonged increase.

One of the hypothesis suggests that glucose combines with an unique receptor, which is located on the beta cell membrane, and activates the release mechanism.

Then the second hypothesis suggests that intracellular metabolite flux occurs through a another pathway such as pentose phosphate shunt, citric acid cycle, or the glycolytic pathway also involved **Matschinsky et al 1968**.

INSULIN SYNTHESIS



Arginine, Leucine, isoleucine and other aminoacids stimulate the insulin secretion **Floyd et al 1966** as do the beta – ketoacids like acetoacetate **Madison et al, 1964**. In addition to this, L-arginine is the another precursor of Nitric oxide, which stimulates insulin secretions.

ii) Hormonal regulation :

Gastro-intestinal hormones:

During the digestion of food, several hormones like gastrin, secretin and pancreozymin were released into the blood, all of which can either stimulate the insulin secretion or enhance the secreting effects of glucose and aminoacids, **Dupre et al 1969.**

Glucagon :

Glucagon from alpha cells of islets, and the same type of cell in the stomach and the duodenum has a potent stimulant effect over beta cells of islets **Samols et al 1965**. Glucagon stimulates insulin secretion not only by the direct action on beta cells that are mediated by the cyclic AMP system **Turtle et al 1967**, but also indirectly by producing hyperglycemia.

Insulin and glucagon regulates the output of glucose from liver by means of competitive antagonism and on the processes concerned with the formation and breakdown of glycogen concerned with gluconeogenesis.

Adenohypophysis :

Hypophysectomy or removal of pituitary gland in rats reduces the insulin secretory capacity of the islets. In man, hypophysectomy or panhypopituitarism is associated with the reduced insulin responses to glucose or arginine. Artificial administration of growth hormone restores the insulin responses to normal condition.

Adrenal cortex :

Adrenelectomy or removal of adrenal gland reduces glucose induced insulin secretion and the amount of cortisol restore the responses to normal level **Malaisse WJ et al,1969**.

Thyroid hormone:

Hypothyroidism depresses the glucose induced insulin secretion and thyroid hormones, T3 and T4 restores the normal response. Hyperthyroidism depletes the islet cells and progressive failure of beta cell functions finally produces metathyroid diabetes. **Houssay.B.A, 1994**.

Placental Hormones :

Pregnancy enhances the glucose induced insulin secretion, probably owing to the secretion of human placental lactogen **Malaisse W.J.et al 1967.**

Oral contraceptives :

Oral contraceptives tend to rise the insulin secretion induced by glucose. Prolonged administration for more than one year may reduce insulin secretion in potentially diabetic women **Spellacy. W. N. et al 1968.**

iii) Neural regulation :

The islets of Langerhans of pancreas are innervated by post ganglionic fibres of the parasympathetic nerve (vagus) and sympathetic divisions of the autonomic nervous system.

Vagal stimulation:

It increases the secretion of insulin by beta cells, mediated by the release of acetyl choline of cholinergic nerve endings proved by **Malaisse W.J.et al 1967.**

Sympathetic nerve stimulation:

It releases noradrenaline locally and splanchnic nerve stimulation releases both adrenaline and noradrenaline hormones from the adrenal medulla and then into the blood stream and to the islets.

These two catecholamine hormones are the only endogenous substances that inhibit glucose or glucagon induced secretion of insulin, **Coore&Randle, 1964**. They do so by stimulating alpha adrenergic receptors over the beta cells.

Noradrenaline and adrenaline also stimulates the beta adrenergic receptors and an action tending to rise the insulin secretion **Porter 1967,** but mostly suppressed by alpha receptor stimulation.

Sympathetic nerve activity also tends to rise the release of glucose from the liver,

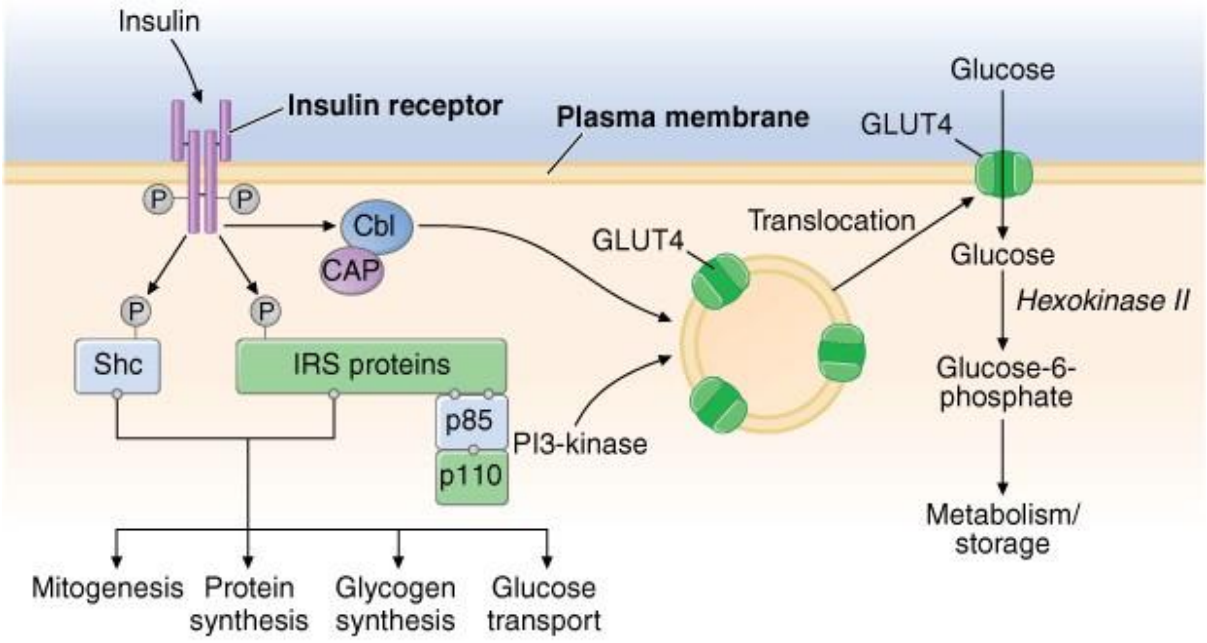
1. By reducing insulin induced glycogenesis,
2. By increasing breakdown of glycogen by catecholamines
3. By release of glucagon and it is the most powerful glycogenolytic agent.

Central nervous system control :

The autonomic nervous system is under central nervous control. During feeding and absorption of foods, vagal activity is increased by excitation of neurons present in the hypothalamus and it elicits an increase in insulin secretion.

During starvation, hypothalamus mediated rise in sympathetic activity via catecholamines and glucagon rise catabolic processes and at the same time insulin secretion is decreased.

INSULIN MECHANISM OF ACTION



MECANISM OF ACTION:

Insulin Receptors:

The insulin receptor is a tetrameric structure made up of two alpha and two beta protein subunits. The human insulin receptor gene is located on the chromosome 19. The alpha subunits binds insulin and where as the beta subunits have intrinsic tyrosine kinase activity **Kido Y et al 2001.**

All the insulin receptors are found upto concentrations of about 20,000 per cell. Binding of the insulin triggers intrinsic tyrosine kinase activity of beta subunits, producing autophosphorylation of beta subunits over tyrosine residues. This autophosphorylation is necessary for insulin to exert biologic effects, also triggers phosphorylation of some cytoplasmic proteins and dephosphorylation, mostly on serine and threonine residues.

When the insulin binds to its receptor, they will aggregate in patches and taken into the cell by receptor mediated endocytosis mechanism. Eventually all the insulin receptor complexes will enter lysosomes and the receptors are broken down or recycled. The insulin receptor has half life of about 7 hours.

ACTIONS OF INSULIN:

The physiologic effects and actions of insulin are complex. The best known effect is the hypoglycemic effect, but

there are additional effects in amino acid and electrolyte transport and in many enzymes and in growth **Salter and Best, 1953.**

The net effect of the hormone is to store carbohydrates, proteins and fats. Therefore this hormone insulin is called the **"Hormone of Abundance".**

RAPID ACTIONS (WITHIN SECONDS)

Insulin increases the transport of glucose, amino acids and potassium into insulin sensitive cells on muscle and adipose tissue. Glucose enters into cells by facilitated diffusion or, in the intestine and kidneys by secondary active transport with sodium ion.

INTERMEDIATE ACTIONS (WITHIN MINUTES)

Insulin promotes protein synthesis in Liver **Elwyn et al A, 1968** and in muscle, it inhibits protein degradation. It also activates glycolytic enzymes and glycogen synthase enzyme **Bishop et al 1965** and inhibits enzyme phosphorylase and gluconeogenic enzymes. The first inhibitory effect of insulin on hepatic glucose release was described by **Madison et al.**

DELAYED ACTIONS (IN HOURS)

Increase in mRNAs for lipogenic enzyme and other enzymes.

INTERMEDIARY METABOLISM OF GLUCOSE

Glucose is the body's major and important energy source during the absorptive state. Most of the absorbed glucose enters cells and it is catabolized into carbondioxide and water, thus providing energy for ATP formation **Feller D et al, 1951.** Skeletal muscle makes up the majority of body mass, so it is the major consumer of glucose in humans even at rest.

Despite these various influences, homeostatic mechanisms operate to maintain a constant level of blood sugar. **Soskin.s.1940.** The normal concentration of blood glucose in fasting state is 60-80 mg per 100ml, but after rich carbohydrate meal, the blood sugar may be elevated up to 140 mg.

In the normal human, a state of "dynamic equilibrium" exists, and the levels of blood sugar are maintained within narrow limits of variation.

The amount of glucose taken out of blood for utilization by the tissues are mostly compensated by the release of glucose into the blood by liver.

Glycogenesis, Glycogenolysis and Gluconeogenesis

After the monosaccharides are absorbed from the intestine into the blood, they may be utilized suddenly by the tissues as a

source of energy or it may be converted into the glycogen and temporarily stored in the liver and muscles.

In the intermediary metabolism of glucose, pyruvic acid, lactic acid, Acetic acid appear as intermediate products during combustion of the glucose into water and carbondioxide.

Glycogenesis, the process of converting blood glucose into liver or muscle glycogen; the hydrolysis of glycogen and this conversion into glucose is called glycogenolysis. Hepatectomized animals land up in severehypoglycemia but have large glycogen stores in their muscles.

This proves that the muscle glycogen cannot be converted into glucose immediately, enough to perform a significant role in maintenance of blood sugar levels.

In normal persons, muscle glycogen is converted indirectly into blood glucose. Part of the lactic acid is produced from the glycogen stores of working muscles,then reaches the liver and is converted into glycogen. Moreover liver is also capable of producing carbohydrate from fatty acids and amino acids by gluconeogenesis **Krebs, H.A.1943.**

This observation of pancreas exerting an influence upon carbohydrate metabolism was quite accidental. Although diabetes mellitus was known to the Romans, this disease was not correlated with hypofunction of the pancreas until 1889.

Von Mering and Minkowski successfully depancreatized a number of dogs to determine the consequent digestive upsets in them. Biochemical analysis demonstrated that the urine sample of these dogs contained large amounts of sugar and that the urine sample from the intact dog did not contain detectable amounts of sugar.

HORMONES AFFECTING BLOOD GLUCOSE LEVEL

Homeostatic effects which keeps the blood glucose value in a remarkably narrow range is due to many factors. There are mainly two types of mutually antagonistic hormones affecting normal blood glucose levels.

- One anabolic hormone, insulin which decreases blood glucose levels.
- Catabolic hormones, glucagon, adrenal corticosteroids, growth hormone, catecholamines and thyroid hormones which increases the blood glucose levels.

Insulin and glucagon are peptide hormones secreted by the beta cells and alpha cells of islets of Langerhans respectively. Pancreatic somatostatin, an another peptide is capable of inhibiting the secretion of both insulin and glucagon and controls growth hormone secretion from the anterior pituitary. Thus somatostatin helps in the local regulation of pancreatic secretion.

Insulin :

On experimental evidence by **Haist in 1944** shows that fasting, fat feeding and insulin administration reduces the need for endogenous insulin and decreases the insulin content of the pancreas by making the islet cells inactive.

Allen in 1922 expressed that the degenerative changes which occur in islet cells of diabetic, partially depancreatized dogs due to over stimulation of the insulin secreting mechanism.

Mirsky in 1942 observed that in partially depancreatized dogs there was a constant hyperglycemic condition due to excessive insulin administration. **Lukens in 1944**, hyperglycemia is the chief causative factor for subsequent failure of pancreas through over work.

Insulin secretion and plasma insulin concentration is increased during the absorptive state when glucose level in blood increases and decreased during post absorptive state.

Glucagon:

The major effects of glucagon occur within the liver and opposite to those of insulin. Glucagon exerts its effects on carbohydrates, fat and protein metabolism to increase plasma glucose levels by stimulating glycogenolysis and gluconeogenesis.

Glucocorticoids:

Cortisol plays a "permissive" role in the adjustments to fasting condition. Plasma cortisol level does not increase much during fasting, but the cortisol in blood maintains the concentrations of key enzymes in liver and adipose tissue utilized for gluconeogenesis and lipolysis. And the overall hyperglycemic effect is due to reduced glucose utilization by many tissues **Ingle 1945**.

Growth hormone:

The effect of growth hormone on metabolism of glucose is an anti-insulin glucose sparing action and to depress glucose uptake by the muscle and adipose tissue and then to stimulate hepatic glycogenolysis **Long.C.N.H.1943**.

Thyroid Hormone:

The overall effects of thyroid hormone on carbohydrate metabolism are much complex **Houssay, B.A., 1944.** It causes an increase in plasma glucose levels by stimulation of glycogenolysis and gluconeogenesis.

At the same time thyroid hormone increases the rate of glucose uptake by cells and it enhance the rate of insulin dependent glycogenesis, all these effects will tend to reduce plasma glucose. Generally, it appears in low concentrations, thyroid hormone is anabolic nature and tends to reduce plasma glucose level while higher doses are catabolic in nature and hyperglycemic.

Catecholamines :

Catecholamines, glucocorticoids, growth hormone and glucagon maintain blood glucose levels during the period of hypoglycemia and it spare the available glucose for the brain **Kendall, E.C.1941.** Rise in plasma glucose is by stimulating glycogenolysis and thereby inhibiting the secretion of insulin.

DIABETES MELLITUS

The term **'Diabetes'** derived from the Greek word which means **"a passer through"** described in the first century. The clinical characteristics of hypofunction of pancreas, diabetes mellitus have been known since the early centuries.

After hypertension, diabetes mellitus is emerging as the most widely contracted disease and also called the **silent killer,** because most diabetics don't even know they have the existence of the disease.

The relationship of diabetes to pancreas and to carbohydrate metabolism was described by the experiments of **Von mering and Minkowski in 1889**. It was described by **Arateus in the first century A.D** as melting down flesh and limbs into urine.

Diabetes mellitus is defined as a state of diminished action of insulin due to its decreased availability and decreased effectiveness in varying combinations, **J.I.Bell and T.D.R.Hockaday.**

Rising trend in prevalence of type 2 diabetes mellitus is associated with many contributory factors including obesity, increased longevity, sedentary life style, unhealthy diet and increased urbanization. Type 2 diabetes mellitus is also commencing at a very early age in many populations, and it is now being observed even in children and adolescents.

Type 2 diabetes mellitus commonly occurs in obese individuals and insulin resistant, but these two factors are not sufficient to cause diabetes mellitus unless accompanied by impaired beta cell function of islets.

Risk Factors:

*** Genetic factors:**

Genetic factors are the most important in the aetiology of type 2 diabetes than type 1 diabetes, as shown by several studies in monozygotic twins where concordance rates for type 2 diabetes mellitus approach over 100%. Over 200 candidate susceptibility genes have been investigated, such as insulin hormone, the receptor of insulin, glycogen synthase and glucose transporters, but there has not been any consistent association of variants in the candidate genes with type 2 diabetes mellitus. Genomic wide researches have been identified the susceptibility genes on chromosome 1q, 12q and 20q, but the causative underlying genes have not been identified yet.

*** Environmental Factors:**

Epidemiological studies of type 2 diabetes mellitus provide evidence that unhealthy eating habits, especially when combined with obesity and decreased physical activity, is well associated with the development of type 2 diabetes.

Although the majority of middle aged diabetic individuals are obese, only a few obese individuals develop diabetes mellitus. Obesity probably acts only as a diabetogenic factor to the insulin action in those who were genetically predisposed to development of type 2 diabetes mellitus.

*** Malnutrition in Utero :**

Retrospective analysis of birth weight in several studies has demonstrated an inverse relationship between birth weight and weight at one year, and the subsequent development of type 2 diabetes in late adulthood age.

It is proposed that malnutrition in intrauterine period may predispose the programme beta cell development and metabolic functions at a critical period, so predisposing to diabetes later in life.

*** Age :**

Age is an important non modifiable risk factor for type 2 diabetes, and it is principally a disease of the middle aged persons and elderly individuals, affecting 10% of the total population over the age of 65 years.

*** Pregnancy :**

During pregnancy, insulin sensitivity is greatly reduced through the action of placental hormones and affects glucose tolerance. The insulin secreting cells of pancreatic islets may be unable to meet this increased demand in pregnant women genetically predisposed to develop diabetes mellitus.

The term 'gestational diabetes mellitus' refers to hyperglycemia occurring for the first time in pregnancy. 80% of the women with gestational diabetes finally leads to development of permanent clinical diabetes requiring treatment.

COMPLICATIONS OF DIABETES MELLITUS

Complications of diabetes mellitus are acute and chronic complications. Risk factors can be modifiable or not modifiable. Overall, the complications are far less severe and less common in people with well-controlled blood sugar levels. However, the non-modifiable risk factors such as age at diabetes onset, type of diabetes, gender and genetics play a role.

ACUTE COMPLICATIONS:

Diabetic Ketoacidosis:

Diabetic ketoacidosis (DKA) is a dangerous and acute complication that is always an emergency and requires prompt medical attention immediately.

Low insulin levels cause the liver to convert fatty acids into ketone for body fuel (i.e., ketosis); ketone bodies are the intermediate substrates in that metabolic sequence. It is normal when periodic, but it can become a serious problem if sustained.

Elevated ketone bodies levels in the blood decrease the blood pH, leading to DKA. The patient in DKA is typically dehydrated, and has rapid and deep breathing. Abdominal pain is also common and may be severe.

The consciousness level is typically normal until late in the process, and then lethargy may progress to coma. Ketoacidosis can become severe enough to cause hypotension, shock, and ultimately death. Urine analysis of DKA patients will reveal significant levels of ketone bodies (which have exceeded their normal renal threshold blood levels to appear in the urine, before other overt symptoms).

Prompt, proper treatment usually results in full recovery of the patient, though death can result from inadequate or delayed treatment, or from severe complications (e.g., brain edema). Ketoacidosis is much more common in type 1 diabetes than type 2 diabetes.

Nonketotic hyperosmolar coma:

Nonketotic hyperosmolar coma is an acute complication sharing many symptoms with DKA, but it is an entirely different origin and different treatment.

A person with very high (above 300 mg/dl (16 mmol/L)) blood glucose levels, water is osmotically withdrawn out of cells into the blood and then the kidneys eventually begins to dump glucose into the urine. This results in loss of water and there is an increase in blood osmolarity.

If fluid is not replaced intravenously, the osmotic effect of high blood glucose levels, combined with the loss of more water, will eventually lead to severe dehydration. The body's cells become progressively and severely dehydrated as water is taken from them and excreted out.

Electrolyte imbalances are also very common and are always dangerous. As with DKA, immediate medical treatment is necessary, beginning with fluid volume replacement. Lethargy may ultimately leads to a coma, though this is more common in type 2 diabetes mellitus than type 1 diabetes mellitus.

Hypoglycemia:

Hypoglycemia, abnormally low blood glucose, is an acute complication of several treatments of diabetes mellitus. It is rare otherwise, either present in diabetic or non-diabetic patients.

The patient may become sweaty, weak, agitated and may have many symptoms of sympathetic over activation of the autonomic nervous system resulting in dread and immobilized panic.

Consciousness levels can be altered or even lost in extreme conditions, leading to seizures, coma, or even brain damage ultimately

leads to death. In patients with chronic diabetes, this may be caused by several factors, as too much or incorrectly calculated and incorrectly timed insulin, too much or incorrectly timed exercise or not enough food intake (specifically glucose containing carbohydrates). The variety of interactions makes cause identification difficult in many circumstances.

Diabetic coma is a threatening medical emergency in which a person with diabetes is comatose because of one of the acute complications of diabetes:

Chronic Complications:

1. Severe hypoglycemia
2. Diabetic ketoacidosis advanced to result in unconsciousness from a combination of severe hyperglycemia, severe dehydration, shock, and exhaustion.
3. Hyperosmolar nonketotic coma cause extreme damage to small blood vessels leading to microangiopathy, which can cause one or more of the following conditions:

- Diabetic nephropathy, a condition cause damage to the kidney which can lead to chronic renal failure and eventually requiring renal dialysis. It is one of the most common cause of adult kidney failure .
- Diabetic neuropathy a condition in which abnormal and decreased sensation, usually in a 'glove and stocking' distribution over the feet but potentially in other nerves, later often fingers and in hands. When it is

combined with damaged blood vessels it can lead to diabetic foot . Other forms of severe diabetic neuropathy may present as mononeuritis or autonomic neuropathy. Another condition, Diabetic amyotrophy is muscle weakness due to neuropathy.

- Diabetic retinopathy, a condition in which growth of friable and poor quality new blood vessels in the retina as well as macular edema, which can lead to severe vision loss or blindness. Globally Retinopathy is one of the most common cause of blindness among non-elderly adults.
- Diabetic encephalopathy is due to increased cognitive decline and dementia, including the Alzheimer's type, observed in diabetes. Various mechanisms are proposed like alterations to the vascular supply of the brain and the interaction of insulin with the brain.
- Diabetic cardiomyopathy causing damage to the heart muscle, causing impaired relaxation and filling of the heart with blood leads to diastolic dysfunction and eventually heart failure occurs, this condition can occur independently of damage done to the blood vessels due to high levels of blood glucose.
- Erectile Dysfunction: The prevalence of erectile dysfunction in men with diabetes mellitus range from 20 to 85 percent and it is defined as consistent inability to have an erection firm enough for having sexual intercourse. Among men with erectile dysfunction, those with diabetes mellitus are likely to have experienced this problem as much as 10 to 15 years earlier than men without diabetes mellitus.

- Periodontal disease or gum disease is associated with diabetes which may make diabetes more difficult to treat this condition. A number of trials have been found improved blood sugar levels in type 2 diabetes mellitus who have undergone the peridontal treatment.

INSULIN RESISTANCE

The concept that insulin resistance may be the underlying cause of type 2 diabetes mellitus was first advanced by Professor Wilhelm Falta and published at University of Vienna in 1931, and confirmed by **Sir Harold Percival Himsworth University College Hospital Medical Centre, London in 1936.** However, type 2 diabetes mellitus does not occur unless there is a concurrent failure of compensatory insulin secretion mechanism.

Insulin resistance is a condition in which the normal amounts of insulin are insufficient to produce a normal insulin response from muscle,fat and liver cells. Insulin resistance in the fat cells results in stored triglycerides hydrolysis which elevates free fatty acid concentrations in the plasma.

Insulin resistance in the muscle reduces glucose uptake, whereas insulin resistance in the liver reduces glucose storage and with both these effects serving to elevate blood glucose levels.

High plasma insulin and glucose levels due to insulin resistance often leads to a condition called metabolic syndrome and type 2 diabetes mellitus.

Insulin resistance is commonly occurring in type 2 diabetes mellitus, hypertension, obesity, polycystic ovarian disease and a numerous genetic syndromes and in many physiological conditions such as puberty and pregnancy **Reucsch JE.**

Insulin resistance is also present in many states of stress, infections, and secondary to treatment with variety of drugs, particularly glucocorticoids. From the molecular perspective, insulin resistance could be either acquired or genetic in nature.

Genetic forms :

Insulin resistance due to genetic defects in insulin and receptor expression and this sequence is relatively rare but highly represents the most severe forms of insulin resistance.

Acquired forms :

Occurs as a result of multiple complex mechanisms. The first one was described that of insulin– receptor down regulation proposed by **Gavin J.R et al 1974.** In addition, there is also an increased serine phosphorylation of the receptor and its corresponding substrate **Zhande R et al.** This leads to a decrease in kinase activity of the insulin receptor and decreased tyrosine phosphorylation of these receptor substrates. The upstream stimulators of these intrinsic kinases may also be multiple.

i) Increased levels of circulating free fatty acids. Free Fatty Acids inhibit insulin stimulated glucose uptake at the level of glucose transport itself, inhibit insulin stimulated glycogen synthesis and inhibit insulin stimulated glucose oxidation proposed by **Roden M et al 1996.**

ii) In obesity, adipose tissue releases a number of factors like Tumor necrosis factor-alpha, various complement related peptides,leptin and two newly discovered hormones resistin and adiponectin also called Acrp 30 and Adipo Q. Tumour necrosis factor alpha leads to the insulin resistance by decreasing intrinsic insulin receptor kinase activity **Hotamisligil GS et al 1996.**Leptin also shown to interfere with insulin the signaling systems in vitro proposed by **Cohen B et al 1996.**

iii) Another set of proteins that can act as inhibitors of intrinsic insulin signalling are the suppressor of cytokine signaling proteins **Emanuelli B et al.** These play a role in acute stress induced states.

iv) Exercise is an another important determinant of insulin sensitivity. Physical inactivity is associated with down regulation of insulin sensitive kinases and it also increases the accumulation of free tatty acids within skeletal muscle.

Sedentary people are therefore become more insulin resistant than active people with the same degree of body mass index. Moreover, physical activity allows non-insulin dependent glucose uptake into the muscles and thereby reducing the demand on the pancreatic beta cells to produce insulin.

v) Diet : Diet is a well known that insulin resistance commonly occurs with obesity. Dietary fat has been implicated as an important driver of insulin resistance. Various studies on animals have been observed that

significant insulin resistance in animals after just 3 weeks on a high fat diet consumption.

Large quantities of saturated as well as monounsaturated and polyunsaturated omega 6 fats all appear to be more harmful to rats to some degree when compared to large amounts of starch, but this saturated fat is the most effective at producing insulin resistance. This is due to direct effects of a high fat diet on blood markers but more significantly high-fat diet has the tendency to result in excess caloric intake that is far in excess of the animals energy needs, resulting in obesity.

Being insensitive to insulin hormone is still positively correlated with the dietary fat intake, and negatively correlated with daily dietary fiber intake but both of these factors are highly correlated with excess body weight. Elevated levels of triglycerides and free fatty acids in the blood stream and tissues was found in many studies to contribute to diminished insulin sensitivity and increased insulin resistance.

Studies have shown that high levels of cortisol within bloodstream from the digestion of the animal protein may contribute to the development of severe insulin resistance. Several studies conclude that high uric acid levels by itself may be a significant cause of insulin resistance.

Vitamin D deficiency is also associated with insulin resistance.

Sedentary lifestyle

Sedentary lifestyle increases the development of insulin resistance. It has been proved that each 500 kcal/week increment in exercise related energy expenditure, reduces the lifetime risk of development of type 2 diabetes by 9%.

Protease inhibitors

Protease inhibitors found in anti retroviral drugs are linked to insulin resistance.

Pancreatic Beta cell failure :

In the early stages of type 2 diabetes mellitus there is only amoderate reduction in the total mass of pancreatic islet tissue. Another hypothesis, yet unproven to explain the beta cell destruction in type 2 diabetes mellitus is that the polypeptide amylin is also secreted together with the insulin, so that in the presence of insulin resistance there is an excessive demand for insulin secretion and also results in the formation of excess amylin and it forms insoluble fibrils of amyloid and it ultimately destroys the beta cells and beta cell numbers are typically to 20-30% in type 2 diabetes mellitus, while alpha cells mass remains unchanged and glucagon secretion is also increased and it contributes to hyperglycemic conditions.

A unifying hypothesis of type 2 diabetes :

Studies of various tissue specific knock out mice suggests a potential unifying hypothesis of insulin resistance as a factor in type 2 diabetes and metabolic syndrome.

Insulin resistance in muscle leads to the accumulation of fats and secondary insulin resistance, hypertriglyceridemia, and increased levels of free fatty acids.

Insulin resistance in the liver leads to increase in hepatic glucose output. Moreover insulin resistance in the human brain leads to an increase in appetite, obesity and further defects in the hepatic glucose output. Finally, insulin resistance in the beta cells leads to a relative insulin deficiency.

Thus insulin resistance in multiple tissues could produce all of the defects associated with type 2 diabetes mellitus and treatment that improves insulin sensitivity would be expected to improve all these defects.

Signs and symptoms :

These depend on variations in individual biology and consequently may not be found with all other people diagnosed with insulin resistance.

- increased hunger
- Lethargy
- Brain fogginess

- High blood sugar levels
- High blood cholesterol levels
- Weight gain, fat storage, difficulty losing weight, excess weight is from of high subcutaneous fat storage, the fat in insulin resistance is generally stored around abdominal organs in both sexes and it is currently suspected that hormones produced in that fatty deposits are the precipitating cause of insulin resistance.
- Increased blood pressure, as many people with hypertension may be either diabetic or prediabetic and have increased insulin levels due to insulin resistance, one of the insulin effects is to control the arterial wall tension throughout the tension in human body.

Associated risk factors:

- Genetic factors
- Family history of type 2 diabetes mellitus
- Insulin receptor mutations like Donohue syndrome
- LMNA mutations like familial partial lipodystrophy
- Cultural variables, such as diet varying with class and race, factors related to chronic stress and socioeconomic status contribute to development of insulin resistance and inhibiting pancreatic function and might be of importance, although this is not fully proved by the scientific evidence.
- Particular environmental factors
- Age more than 40 years

- Obesity
- The tendency to store fat preferentially in the abdomen also known as "abdominal obesity".
- Sedentary lifestyle, lack of physical activity
- Hypertension
- Hypertriglyceridemia
- Low level of high density lipoprotein also known as HDL cholesterol
- Prediabetes, in which blood glucose levels have been too much elevated in the past and the patient's body has previously shown problems with its production and usage of insulin and the previous evidence of impaired glucose homeostasis
- Gestational diabetes during past pregnancies and giving birth to a baby weighing more than four kilograms.

Pathology:

- Obesity and overweight (Body Mass Index> 25)
- Metabolic syndrome like hyperlipidemia with HDL cholesterol level less than 0.90 mmol/L or triglyceride level more than 2.82 mmol/L, hypertension with blood pressure more than 140/90 mmHg or arteriosclerosis
- Any Liver pathology
- Infections mainly Hepatitis C
- Hemochromatosis

- Gastroparesis
- Polycystic ovary syndrome
- Hypercortisolism features like Cushing's syndrome and patients receiving glucocorticoid therapy
- Medications like glucosamine, rifampicin, isoniazid,risperidone, progestogens, glucocorticoids, methadone and many antiretroviral drugs.

Molecular mechanism :

Insulin resistance denotes that the body's cells lose sensitivity to insulin hormone which was secreted by the pancreas to promote glucose utilization.

At the molecular level mechanism, a cell senses insulin through the insulin receptors, with signal propagating through a prompt cascade of molecules known as PI3K/Akt/mTOR signaling pathway.

Recent studies have shown that this pathway may operate as a bistable switch under various physiologic conditions for certain types of cells, and insulin related responses may be a threshold phenomenon. These pathway's sensitivity to insulin may be attenuated by many factors such as free fatty acids which may causing insulin resistance.

From a broader perspective, however, sensitivity tuning is a common practice for an animal to adapt to the sudden changing environment or many metabolic conditions like pregnancy which is a prominent change of most of all metabolic conditions, under which the

mother has to reduce her insulin sensitivity to spare more glucose for the brain uptake.

This can be achieved through raising the response threshold like postponing the onset of sensitivity by secreting placental growth factors to interfere with the interaction between insulin receptor substrate and PI3K, which is an important of the so called the adjustable threshold hypothesis of insulin resistance.

Cellular level :

At the cellular level, the variance in insulin sensitivity between nondiabetic humans may be explained by two mechanisms as differences between phospholipid profiles of skeletal muscle cell membranes and in intra myocellular lipid stores within these cells.

Very high levels of lipids in the blood stream results in accumulation of triglycerides and their derivatives within muscle, which activates proteins Kinase, ultimately reducing the glucose uptake at any given insulin levels.

This mechanism is fast acting and it induce insulin resistance within days or even upto hours in response to a large lipid influx.

Draining the intracellular reserves is more challenging, moderate caloric restriction alone or even over a period of several months appears to be ineffective and it must be combined with physical exercise to have improved effect.

At a molecular level, insulin resistance has been the factor to be a reaction to excess nutrition by superoxide dismutase in cell mitochondria and it acts as an antioxidant defense mechanism.

This seems to exist under diverse causes of insulin resistance. It is also based on the finding that insulin resistance may be rapidly reversed by exposing cells to the mitochondrial uncouplers, electron transport chain inhibitors and mitochondrial superoxide dismutase mimetics.

One of the primary treatment for insulin resistance is increase in physical activity like exercise and weight loss. Research shows that a low carbohydrate and high fibre diet may help.

Drugs like metformin and thiazolidinediones improve insulin resistance, but they are approved therapies for type 2 diabetes only, not for insulin resistance. Growth hormone replacement therapy may be the another cause for increased insulin resistance.

Insulin resistance is associated with abnormalities in lipid profiles, particularly high blood triglycerides and low high density lipoprotein levels.

The Diabetes Prevention Program showed that exercise and healthy diet were as much as effective as metformin at reducing the risk of progression to type 2 diabetes mellitus.

One study on 2009 found that carbohydrate deficit after physical activity, but not the energy deficit which contributed to insulin sensitivity increase.

Resistant starch from high amylase content corn, amylomaize has been shown to significantly reduce insulin resistance in healthy individuals, also in individuals with insulin resistance and in individuals with type 2 diabetes mellitus. Many animal studies demonstrate that this cannot reverse damage already done by high blood glucose levels, but it reduces insulin resistance level and reduces the development of further damage to the body.

Some types of polyunsaturated fatty acids may moderate the progression of insulin resistance into type 2 diabetes mellitus, however, omega 3 fatty acids appear to have minimal ability to reverse insulin resistance and they cease to be the efficacious once type 2 diabetes mellitus is established.

Caffeine intake limits insulin action, but not enough to increase blood sugar levels in healthy persons.

Complications :

- Macrovascular complications leads to cardiovascular disease for which the accelerated atherosclerosis is a contributor of Coronary artery disease, leading to angina or myocardial infarction also known as heart attack.

- Diabetic myonecrosis causing muscle wasting.
- Peripheral vascular disease, which contributes to intermittent claudication causing exertion related leg and foot pain as well as diabetic foot.
- Stroke mainly the ischemic type.

- Carotid artery stenosis does not occur more in diabetes, and there appears to be a very low prevalence of abdominal aortic aneurysm. However, diabetes mellitus does cause higher morbidity, mortality and higher operative risks with these conditions.
- Diabetic foot, due to a combination of sensory neuropathy with numbness or insensitivity and vascular damage, increases rates of skin ulcers called diabetic foot ulcers and infections and, in serious cases, necrosis and gangrene occurs. This is why it takes longer for diabetics to heal from leg and foot ulcers and thus diabetics are prone to leg and foot infections. In the developed world, it is the most common cause of non traumatic adult amputation, usually of toes and or feet.
- Female infertility is more common in women with type 1 diabetes, despite modern treatment and also delayed puberty and menarche, many menstrual irregularities especially oligomenorrhoea, polycystic ovarian syndrome, mild hyperandrogenism and possibly earlier menopause occurs.

- The immune response mechanism is impaired in individuals with diabetes mellitus. Many Cellular studies have shown that hyperglycemia both reduces the functions of immune cells and increases the inflammation.
- Prevalence of many respiratory infections such as pneumonia and influenza are more common among individuals with diabetes mellitus. Lung functions are altered by vascular disease and inflammation, which ultimately leads to an increase in susceptibility to respiratory agents. Several studies have shown that diabetes associated with a worse disease course and very slow recovery from respiratory infections.
- Restrictive lung disease is very common and known to be associated with diabetes. Lung restriction in diabetes mellitus could results from chronic low grade tissue inflammations, microangiopathy, and accumulation of advanced glycation end products in the lungs. In fact the presence of restrictive lung defect in association with diabetes mellitus have been shown even in presence of severe obstructive lung diseases like asthma and Chronic obstructive lung diseases in diabetic patients.
- Mental Depression was associated with diabetes in a 2010 study of 4,263 individuals with type 2 diabetes mellitus, followed from 2005 to 2007. They were found that there was a statistically significant association with mental depression and a high risk for micro and macro vascular events.

MATERIALS AND METHODS

MATERIALS AND METHODS

PLACE OF STUDY

Study was conducted in the Institute of Physiology, Madurai Medical College, Madurai and Department of Biochemistry, Madurai Medical College, Madurai for a period of six months.

ETHICAL COMMITTEE

Approval obtained from the ethical committee of Government Rajaji Hospital, Madurai.

STUDY DESIGN

Observational case control study

SAMPLE SIZE

Total subjects - 150

Study population - 100

Controls - 50

STUDY POPULATION

Apparently healthy young adults aged between 18 and 21 years, both male and female were included in this study

SDP Group : Offspring of single diabetic parent.

BDP Group : Offspring of both diabetic parents.

CONTROL GROUP

NDP Group : Offspring of non diabetic parents.

INCLUSION CRITERIA:

1. Age between 18 – 21 years.

2. Fasting and postprandial blood sugar within normal limits.

Fasting blood sugar <126mg/dl

Post prandial blood sugar< 200 mg/dl

EXCLUSION CRITERIA:

1. Obesity (BMI > 25kg/ m^2)

2. Polycystic ovarian syndrome,

3. On long term drugs like

- Steroids,
- Metformin.

4. H/o systemic diseases like

- Diabetes mellitus,
- Endocrinopathies like Cushing's syndrome etc.,
- Liver disease,
- Renal disease,

5. Nicotine dependence or alcohol use disorder.

6. Pancreatitis.

MATERIALS USED FOR STUDY

1. Proforma – to record the anthropometric measurements and the clinical findings of the subjects.

2. Portable weighing machine – to record the body weight in kilograms.

3. Inch tape – to measure the standing height in centimeters and waist-hip circumference measurements in centimeters.

4. Standardized mercury sphygmomanometer – to record the Blood Pressure in mmHg.

5. Fasting venous blood sample – to estimate fasting blood sugar and fasting insulin levels.

METHODOLOGY

The study was initiated after obtaining permission from Dean, Madurai Medical College, Madurai.

150 young healthy volunteers aged between 18- 21 years were selected according to the Inclusion and Exclusion Criteria and categorised into three groups based on the parental history from medical students of Madurai Medical College, Madurai.

After getting informed written consent from the subjects, detailed history was taken. General and Systemic examinations was done. Blood sample was collected following overnight fasting of 10 hours.

The experimental protocol includes

1. RECORDING OF A DETAILED HISTORY

including history of present illness

H/o Systemic Illness

- Diabetes mellitus
- Hypertension
- Thyroid disorders and other endocrine abnormalities
- Liver disease
- Renal disease
- Cardiovascular disease
- Respiratory disorders

- Neuromuscular disorder
- Family history :
    - Family history of Father having Diabetes Mellitus

      - Duration in years**:**

      -Duration of treatment**:**
    - Family history of Mother having Diabetes

      Mellitus

      -Duration in years**:**

      -Duration of treatment**:**
- Personal history :
    - Smoking,
    - Alcoholism,
    - Diet history..
- Drug history:

  H/o taking steroids
  H/o taking hypoglycemic agents
  H/o taking androgens

2. MEASUREMENT OF ANTHROPOMETRIC INDICES:

The subjects were asked to stand erect with their arms relaxed at their side and feet together.

The following were measured:

Weight (in kilograms) was recorded using a portable standard weighing machine.

Height (in centimeters) was measured to the nearest 0.5 cm using an inch tape.

Body Mass Index (BMI) was calculated using Quetelet's Index.

BMI = Weight (Kg)/ Height (m^2).

Waist hip circumference ratio According to the World Health Organisation's data gathering protocol, the waist circumference should be measured at the midpoint between the lower margin of the last palpable ribs and the top of the iliac crest, using a stretch-resistant tape that provides as constant 100 g tension. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor. For both measurements, the individual should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing. The subject should be relaxed, and the measurements should be taken at the end of a normal respiration

3. RECORDING OF VITAL SIGNS viz. pulse rate, respiratory rate and measurement of blood pressure were done and documented.

4. **GENERAL EXAMINATION** was done to elicit Pallor, Cyanosis, Icterus, Clubbing, Pedal edema, Jugular venous pulse.

5. **SYSTEMIC EXAMINATION** of cardiovascular system, respiratory system and central nervous system was done to assess the health of the subject.

6.BLOOD INVESTIGATIONS:

Fasting blood samples were collected in the morning between 7 a.m. and 8 am by venipuncture with all aseptic precautions, using a dry disposable syringe under sterile conditions in a sterile plain vial. Serum was separated by centrifugation at 3000 rpm for 15 minutes and is used for estimation of fasting blood sugar level and fasting insulin levels.

ESTIMATION OFFASTING BLOOD GLUCOSE:

METHOD:

GOD-POD method (Glucose oxidase peroxidase method) specific for glucose.

PRINCIPLE:

Glucose is oxidized by glucose oxidase to give gluconic acid and hydrogen peroxide. The hydrogen peroxide that is formed is broken down by peroxidase to water and oxygen. Oxygen oxidizes phenol which combines with 4 amino antipyrine to give pink colored complex. The intensity of colored complex is measured calorimetrically at 515nm which is directly proportional to concentration of glucose.

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GOD}} \text{Gluconic acid} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + 4\ \text{Aminoantipyrine} \xrightarrow{\text{POD}} 4H_2O + \text{Colored quinone}$$

GOD – Glucose oxidase

POD - Peroxidase

PROCEDURE:

	Blank B	Standard S	Sample T
Distilled water	10µL	-	-
Standard	-	10µL	-
Sample	-	-	10µL
Working reagent	1000µL	1000µL	1000µL

Mix the content of the test tube thoroughly and keep them for 15 minutes. Measure the optical density using calorimeter at 515nm. Final color complex is stable for more than 1 hour.

CALCULATION:

Concentration of standard = 100mg/dl.

Sugar present in 100 ml of plasma/ serum =

$$= \frac{\text{OD TEST - OD BLANK}}{\text{OD STD} - \text{OD BLANK}} \boldsymbol{X} \frac{\text{CONC OF STD}}{\text{VOLUME OF SAMPLE}} \boldsymbol{X} 100$$

$$= \frac{\text{OD TEST - OD BLANK}}{\text{OD STD} - \text{OD BLANK}} \boldsymbol{X} \frac{0.01}{0.01} \boldsymbol{X} 100$$

$$= \frac{\text{OD TEST - OD BLANK}}{\text{OD STD} - \text{OD BLANK}} \boldsymbol{X}\ 100\text{mg/dl}$$

General Parameter:

- Reaction type : End point
- Standard concentration : 100 mg/dl
- Linearity is up to 500 mg/dl
- If sample value is 500mg/dl ,dilute the sample 1:2 with distilled water & repeat assay

Result :

Amount of glucose present in 100 ml of plasma/ serum = ----------mg/dl

Conversion:

Glucose in mmol/L = Glucose in mg/dl x 0.0555

REFERENCE VALUE:

ADA GUIDELINES (2011) FOR BLOOD SUGAR LEVEL

	Normal mg/dl	**Impaired mg/dl**	**Diabetes mg/dl**
Fasting	70 - 99	100 - 125	≥ 126
2hrs Post prandial	Upto 140	140 - 199	≥200
Random	80 – 120		≥200

ESTIMATION OF FASTING INSULIN:

The **DRG Insulin Enzyme Immunoassay Kit** provides materials for the quantitative determination of Insulin in serum and plasma (Heparin- or Citrate-plasma).

This assay is intended for in vitro diagnostic use only.

METHOD:

ELISA – Enzyme linked immunosorbent assay method.

PRINCIPLE:

The DRG Insulin ELISA Kit is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle.

The microtiter wells are coated with a monoclonal antibody directed towards a unique antigenic site on the Insulin molecule.

An aliquot of patient sample containing endogenous Insulin is incubated in the coated well with enzyme conjugate, which is an anti-Insulin antibody conjugated with Biotin. After incubation the unbound conjugate is washed off.

During the second incubation step Streptavidin Peroxidase Enzyme Complex binds to the biotin-anti-Insulin antibody.The amount of bound HRP complex is proportional to the concentration of Insulin in the sample.

Having added the substrate solution, the intensity of colour developed is proportional to the concentration of Insulin in the patient sample.

PROCEDURE:

All standards, samples, and controls should be run in duplicate concurrently so that all conditions of testing are the same.

1. Secure the desired number of Microtiter wells in the holder.
2. Dispense **25 µl** of each Standard, controls and samples with new disposable tips into appropriate wells.
3. Dispense **25 µl** Enzyme Conjugate into each well.
4. Thoroughly mix for 10 seconds. It is important to have a complete mixing in this step.
5. Incubate for **30 minutes** at room temperature without covering the plate.
6. Briskly shake out the contents of the wells.

   Rinse the wells 3 times with diluted Wash Solution (400 µl per well). Strike the wells sharply on absorbent paper to remove residual droplets.

Important note:

The sensitivity and precision of this assay is markedly influenced by the correct performance of the washing procedure!

1 Add **50 µl** of Enzyme Complex to each well.

2 Incubate for **30 minutes** at room temperature.

3 Briskly shake out the contents of the wells.

Rinse the wells 3 times with diluted Wash Solution (400 µl per well). Strike the wells sharply on absorbent paper to remove residual droplets

4 Add **50 µl**of Substrate Solution to each well.

5 Incubate for **15 minutes** at room temperature.

6 Stop the enzymatic reaction by adding **50 µl** of Stop Solution to each well.

7 Read the OD at **450±10 nm** with a microtiter plate reader **within 10 minutes** after adding the Stop Solution.

Calculation of Results of insulin level:

1. Calculate the average absorbance values for each set of standards, controls and patient samples.
2. Construct a standard curve by plotting the mean absorbance obtained from each standard against its concentration with absorbance value on the vertical(Y) axis and concentration on the horizontal (X) axis.
3. Using the mean absorbance value for each sample determine the corresponding concentration from the standard curve.
4. Automated method: Computer programs using cubic spline, 4 PL (4 Parameter Logistics) or Logit-Log can generally give a good fit.
5. The concentration of the samples can be read directly from this standard curve. Samples with concentrations higher than that of the

highest standard have to be further diluted. For the calculation of the concentrations this dilution factor has to be taken into account.

ESTIMATION OF INSULIN RESISTANCE

HOMEOSTATIC MODEL ASSESSMENT OF INSULIN RESISTANCE

In the late 1970s, Turner and coworkers constructed a mathematical model to predict the interaction of two potential determinants of glycemia in diabetic patients, namely, insulin deficiency and insulin resistance. It was termed the homeostatic model assessment(HOMA).

Homeostasis model assessment was first developed in 1985 by Matthews *et al*. It is a method used to quantify insulin resistance and beta-cell function from basal (fasting) glucose and insulin (or C-peptide) concentrations. HOMA-IR is a model of the relationship of glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and β-cell function. Insulin levels depend on the pancreatic β-cell response to glucose concentrations while, glucose concentrations are regulated by insulin-mediated glucose production via the liver. Thus, deficient β-cell function will echo a diminished response of β-cell to glucose-stimulated insulin secretion. Similarly, insulin resistance is reflected by the diminished suppressive effect of

insulin on hepatic glucose production. The HOMA-IR model has proved to be a robust clinical and epidemiological tool for the assessment of insulin resistance. HOMA-IR describes this glucose-insulin homeostasis by means of a set of simple, mathematically-derived nonlinear equations. The approximating equation for insulin resistance has been simplified; it uses a fasting blood sample. It is derived from the use of the insulin-glucose product, divided by a constant. The product of FPG × FPI is an index of hepatic insulin resistance.

HOMA – IR Index

$$= \frac{\textbf{Fasting Insulin(mU/ml) x Fasting Plasma glucose(mg/ dl)}}{\textbf{405}}$$

It is a simpler, cheaper, less labor-intensive, less time consuming and more acceptable to young people and more practical method for application in large epidemiologic studies.

According to Resources for Gastroenterology and Hepatology Of India, HOMA-IR value ,

Less than 2.60 - High insulin sensitivity,

2.60 – 3.80 - Borderline,

More than 3.80 - Insulin resistance.

RESULTS AND OBSERVATION

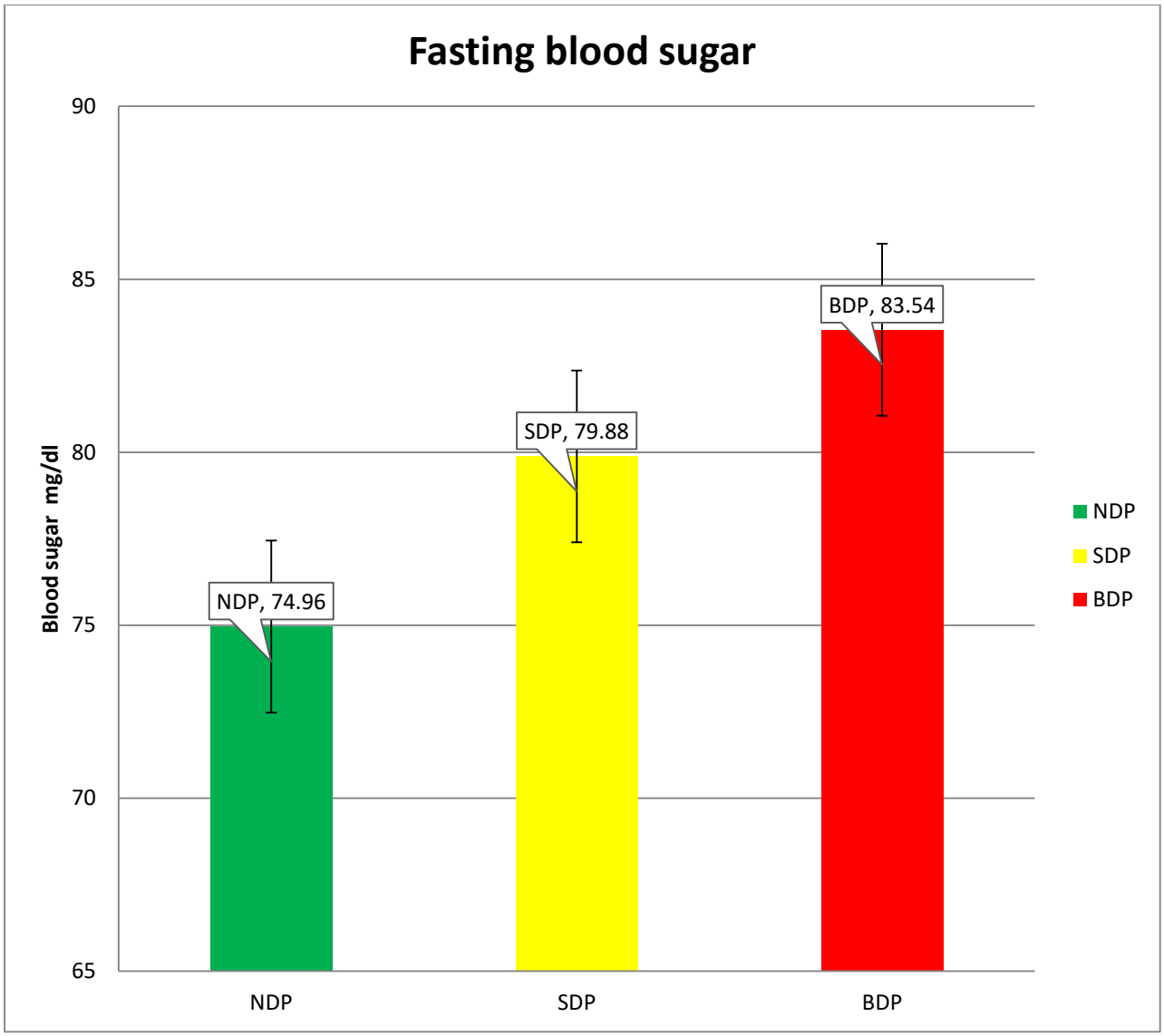
RESULTS AND OBSERVATION

Data was entered and analyzed using **SPSS (Statistical Package for Social Sciences) software version 16**, Mean was compared across all three groups using one way ANOVA (Analysis of Variance), after findings of significance of ANOVA, a multiple comparison between pair of means were made using the Scheffe method of multiple pair wise comparison, a p-value <0.05 was considered as significant as differences in means of two groups.

Pearson correlation coefficient test was used to see the correlations among waist hip ratio and HOMA- IR, among all three groups independently, a correlation test p-value <0.05 considered as significant correlation between two parameters.

Bar charts were used to display the means and percentages across the three study groups.

1. FASTING BLOOD SUGAR:

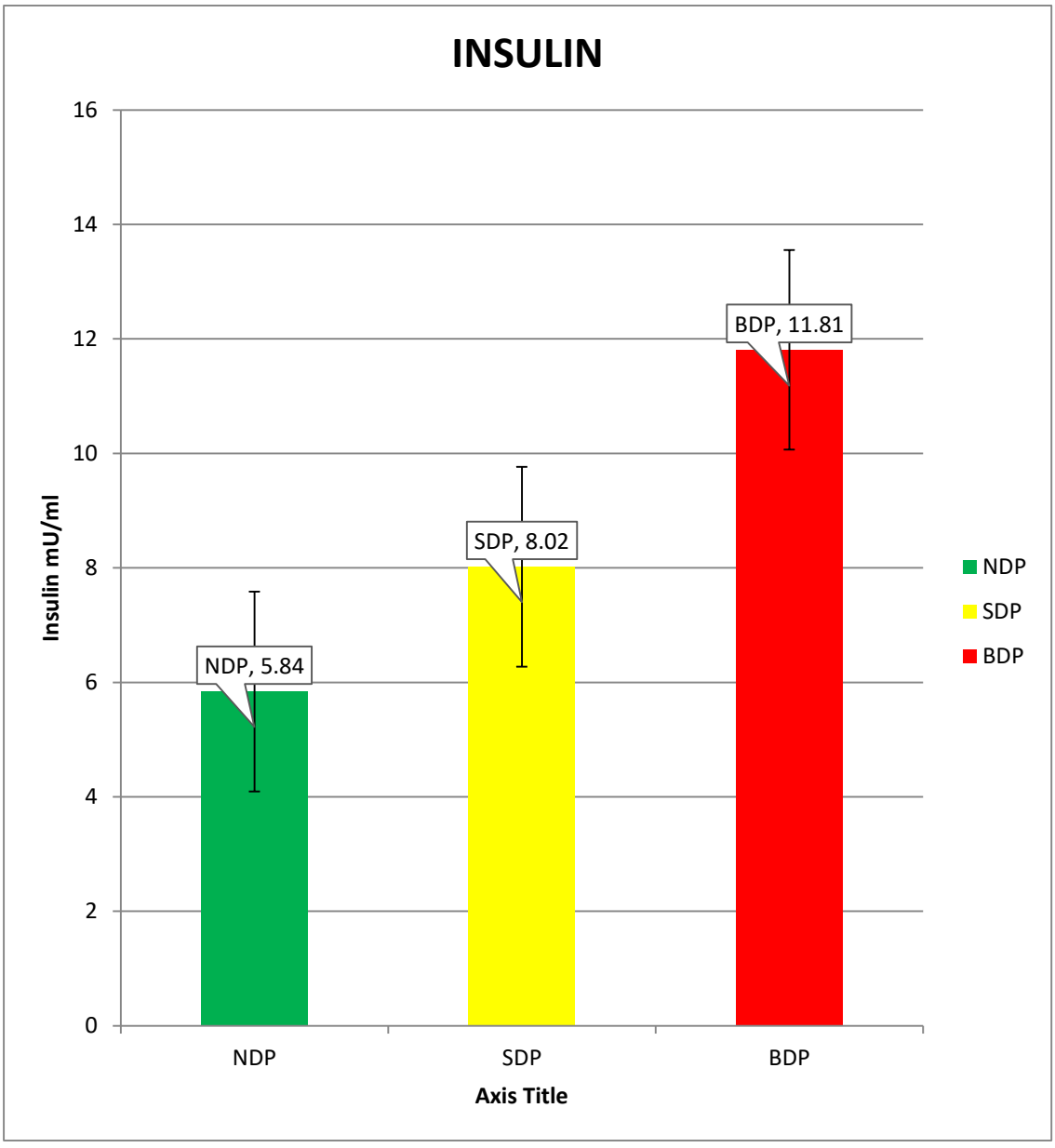


1. FASTING BLOOD SUGAR:

Study group	Number of subjects	Fasting Blood Sugar (mg/dl)		p Value
		Mean	Standard deviation	
NDP	50	74.96	4.89	**p=0.0001 significant**
SDP	50	79.88	5.47	
BDP	50	83.54	5.7	

Table 1 shows mean fasting blood sugar levels of NDP, SDP and BDP groups as 75.6, 80.8 and 83.5 respectively. Statistical analysis using ANOVA shows significant difference, p value = 0.0001.

2. FASTING INSULIN LEVEL:

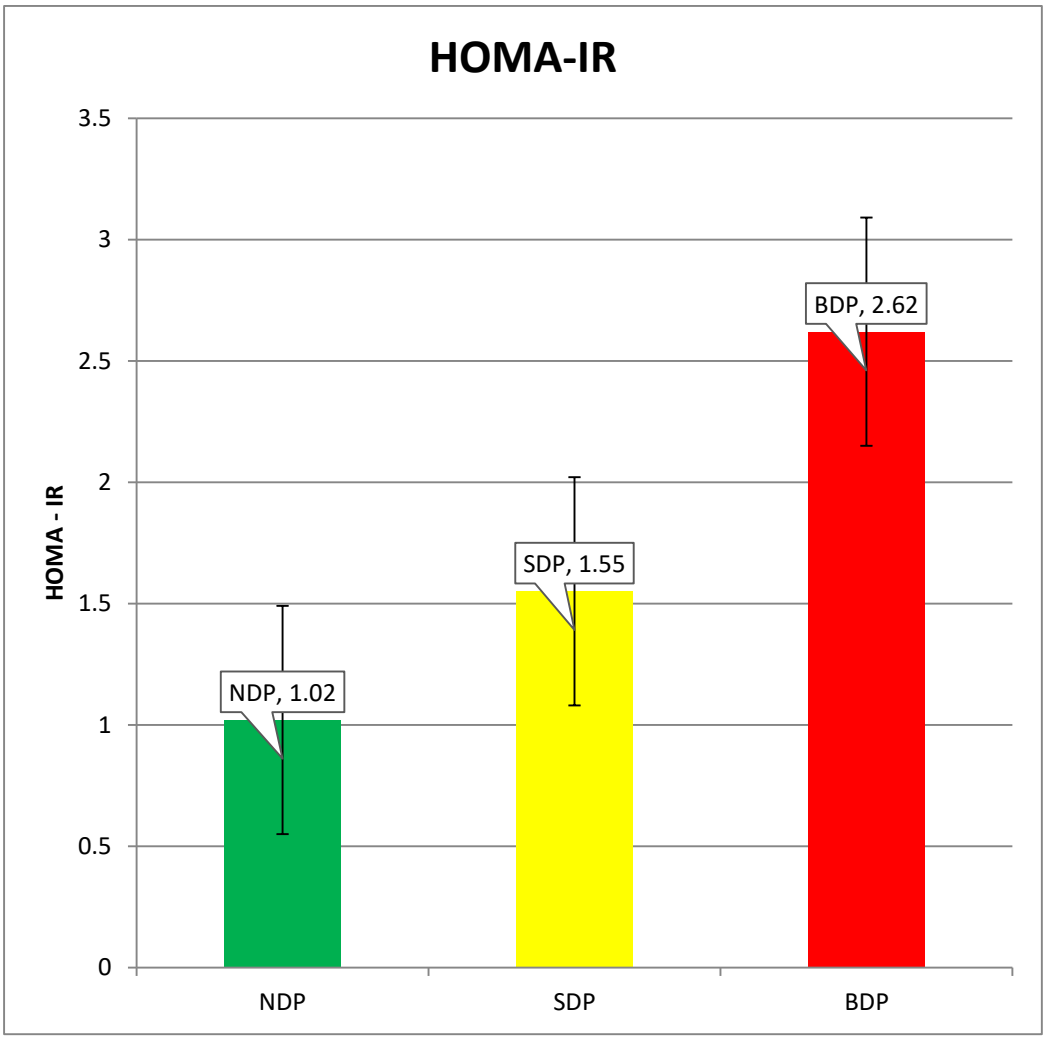


2. FASTING INSULIN LEVEL:

Study group	Number of subjects	Insulin level (mU/ml)		p Value
		Mean	Standard deviation	
NDP	50	5.84	1.56	**p=0.0001 significant**
SDP	50	8.02	1.66	
BDP	50	11.81	3.32	

Table 2 shows mean fasting insulin levels of NDP,SDP and BDP groups as 5.84, 8.02 and 11.81 respectively. Statistical analysis using ANOVA shows significant difference, p = 0.0001.

3. COMPARISON OF HOMA – IR AMONG THREE GROUPS:

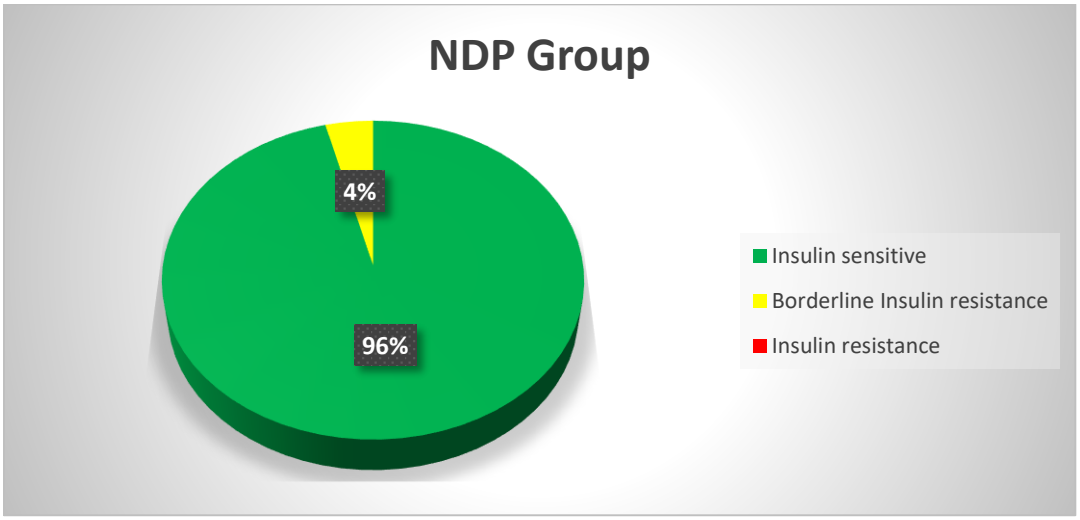
- 

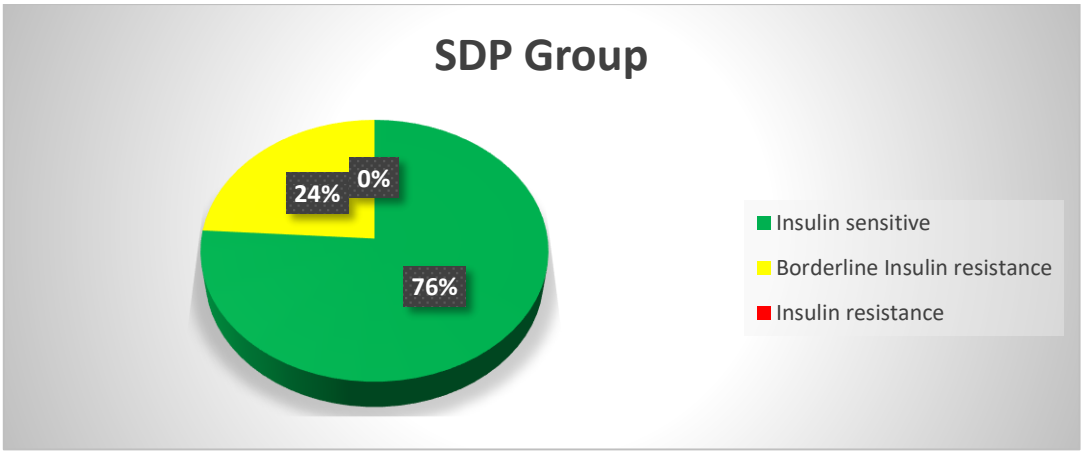
3. COMPARISON OF HOMA – IR AMONG THREE GROUPS:

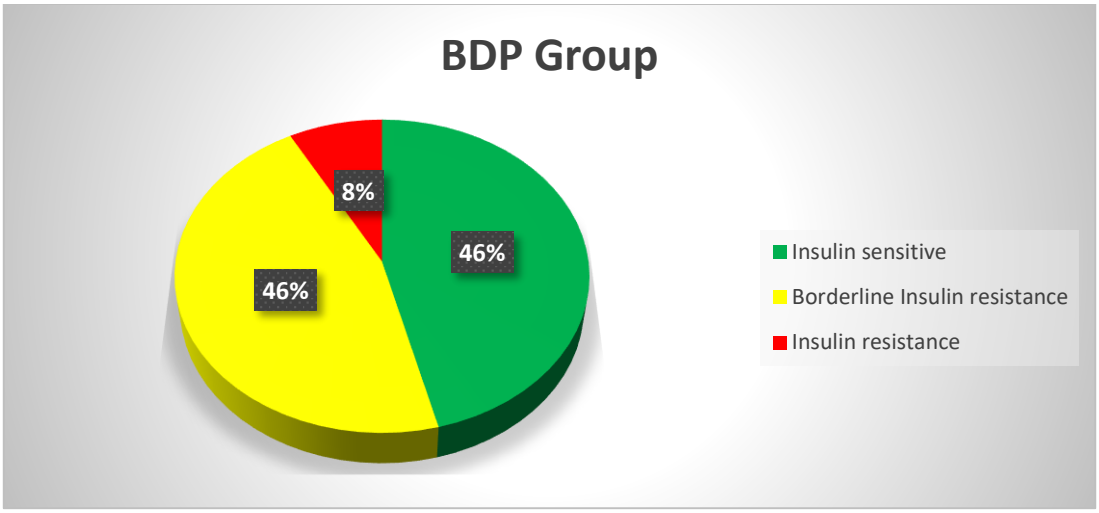
Study group	Number of subjects	HOMA – IR		p Value
		Mean	Standard deviation	
NDP	50	1.02	0.31	**p=0.0001 significant**
SDP	50	1.55	0.34	
BDP	50	2.62	0.82	

Table 3 shows mean HOMA- IR values of three groups and the mean value of NDP group is 1.05, SDP group is 1.59 and BDP group is 2.62. Results analysed using ANOVA disclosed a statistically **significant 'p' value.**

4. DISTRIBUTION OF INSULIN RESISTANCE AMONG 3 GROUPS:





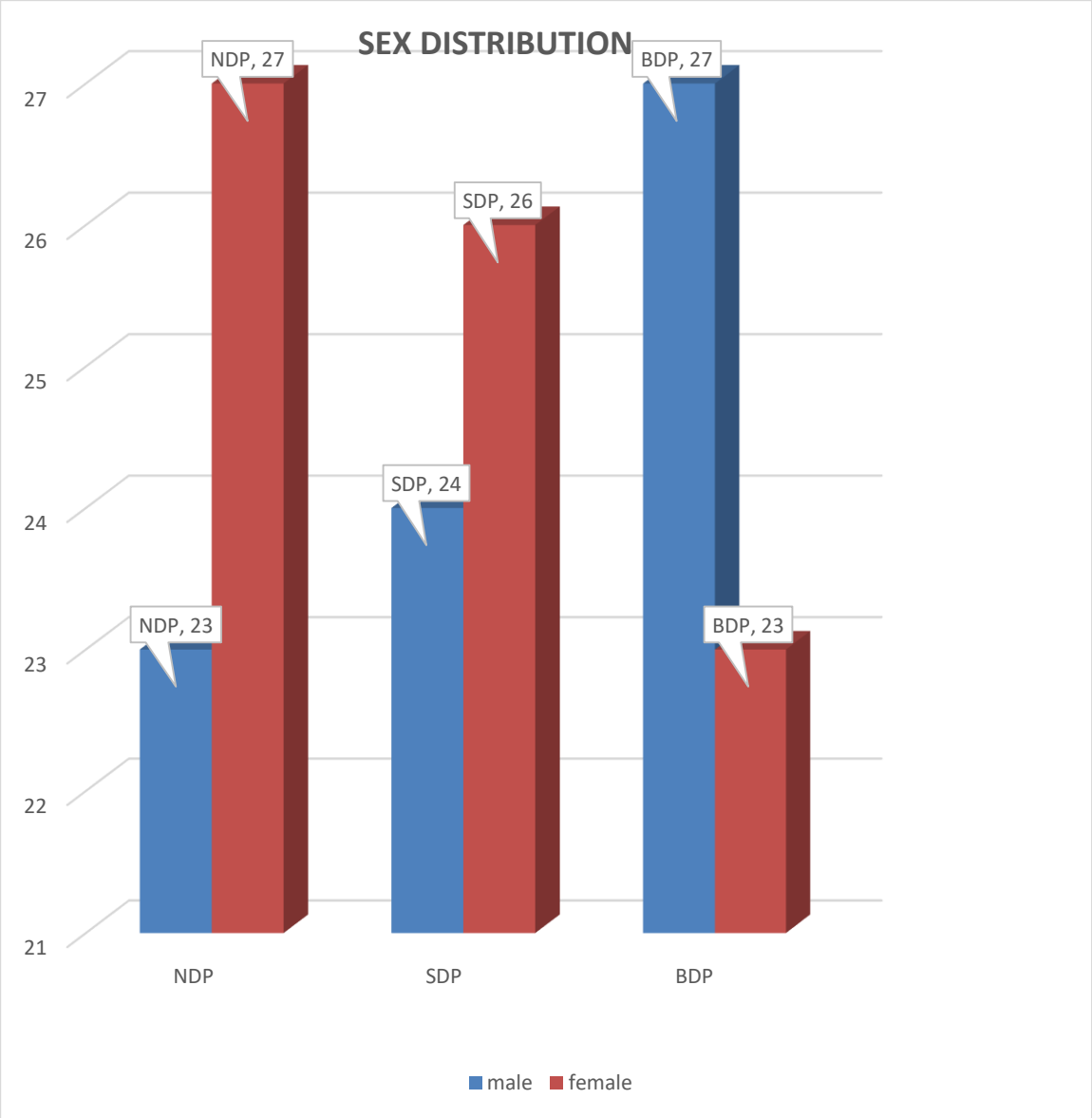


4. DISTRIBUTION OF INSULIN RESISTANCE AMONG 3 GROUPS:

HOMA – IR	NDP	SDP	BDP
Insulin sensitive <2.6	48	38	23
Borderline Insulin resistance 2.6 - 3.8	2	12	23
Insulin resistance >3.8	0	0	4

Table 4 shows the insulin resistance levels among 3 groups. In NDP group only 4% of subjects have borderline insulin resistance, in SDP group 24% of subjects have borderline insulin resistance and in BDP group 8% of subjects have insulin resistance and 46% of subjects have borderline insulin resistance.

5. SEX DISTRIBUTION :

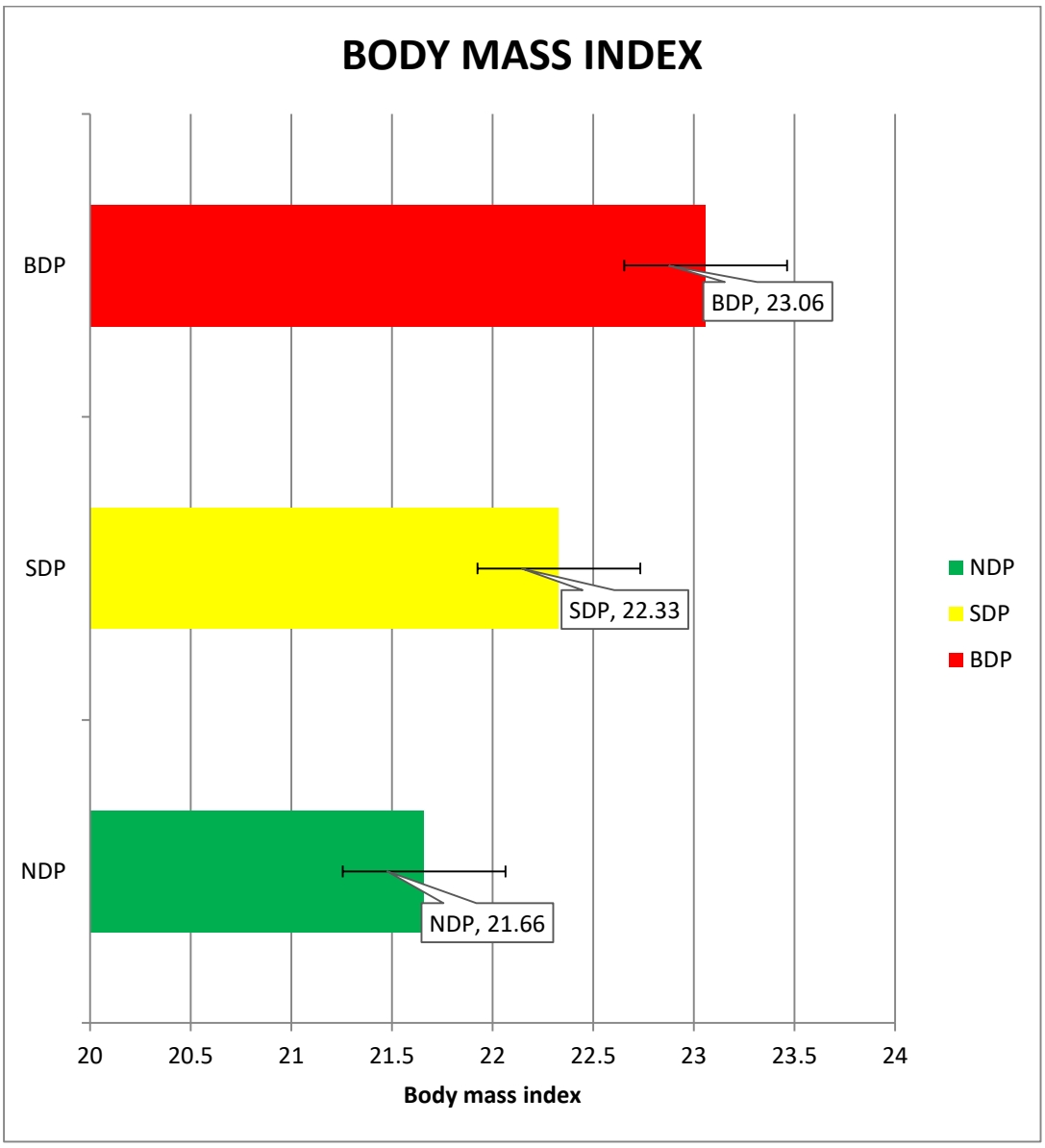


5. SEX DISTRIBUTION :

STUDY GROUP	MALE	FEMALE	TOTAL
NDP	23	27	50
SDP	24	26	50
BDP	27	23	50
TOTAL	74	76	150

Table 5 shows the sex distribution in all three groups. Totally 74 male and 76 female were included in this study.

6 .BODY MASS INDEX:

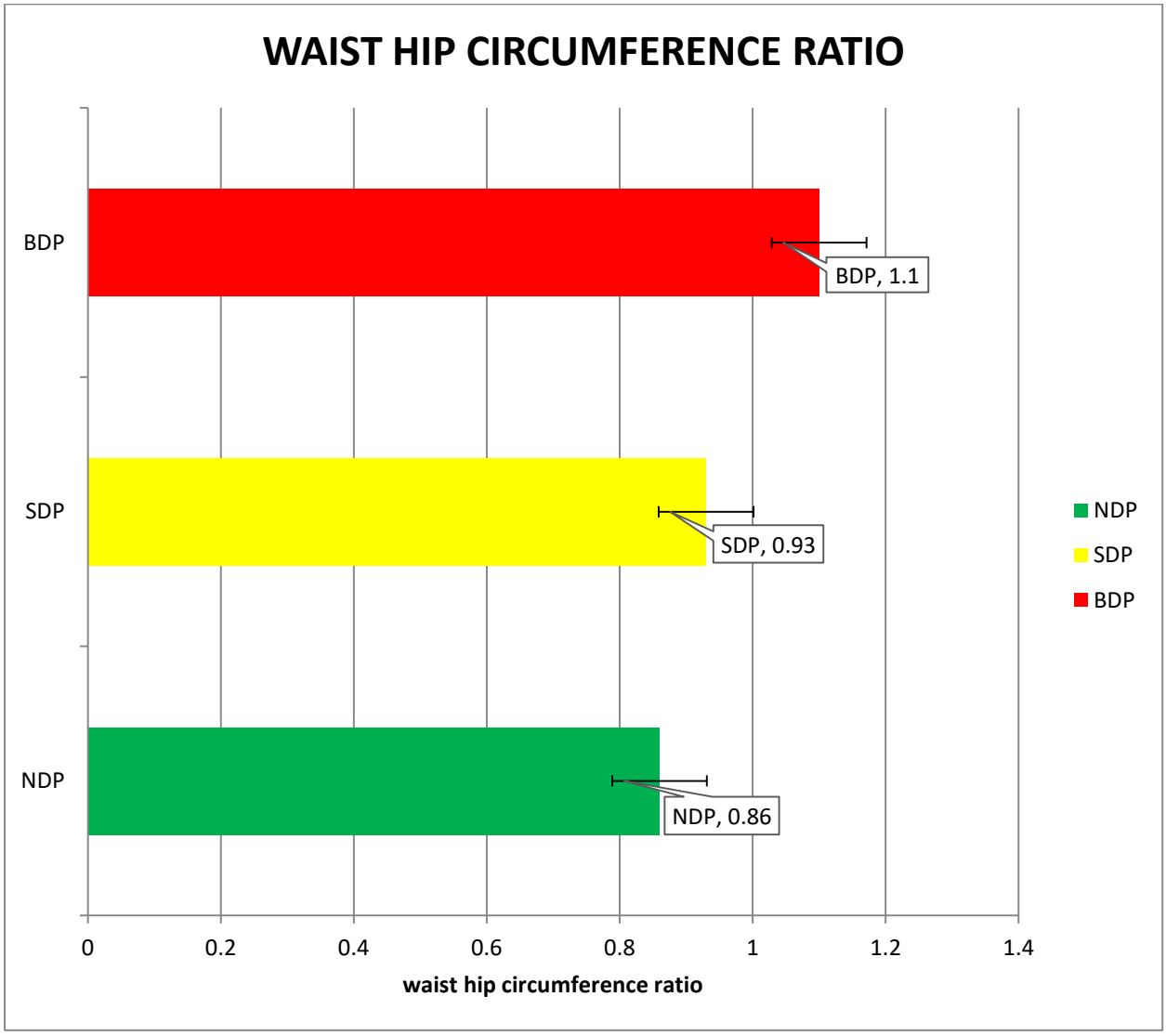


6. BODY MASS INDEX:

Study group	Number of subjects	Body mass index		p Value
		Mean	Standard deviation	
NDP	50	21.66	2.08	**p=0.0012 significant**
SDP	50	22.33	1.91	
BDP	50	23.06	1.7	

Table – 6 showing mean BMI value of offspring of non diabetic parent group (NDP), offspring of single diabetic parent group (SDP) and offspring of both diabetic parent group (BDP) as 21.66, 22.33 and 23.06 respectively. By using ANOVA, p Value is 0.0012 which is statistically significant.

7. WAIST HIP CIRCUMFERENCE RATIO:



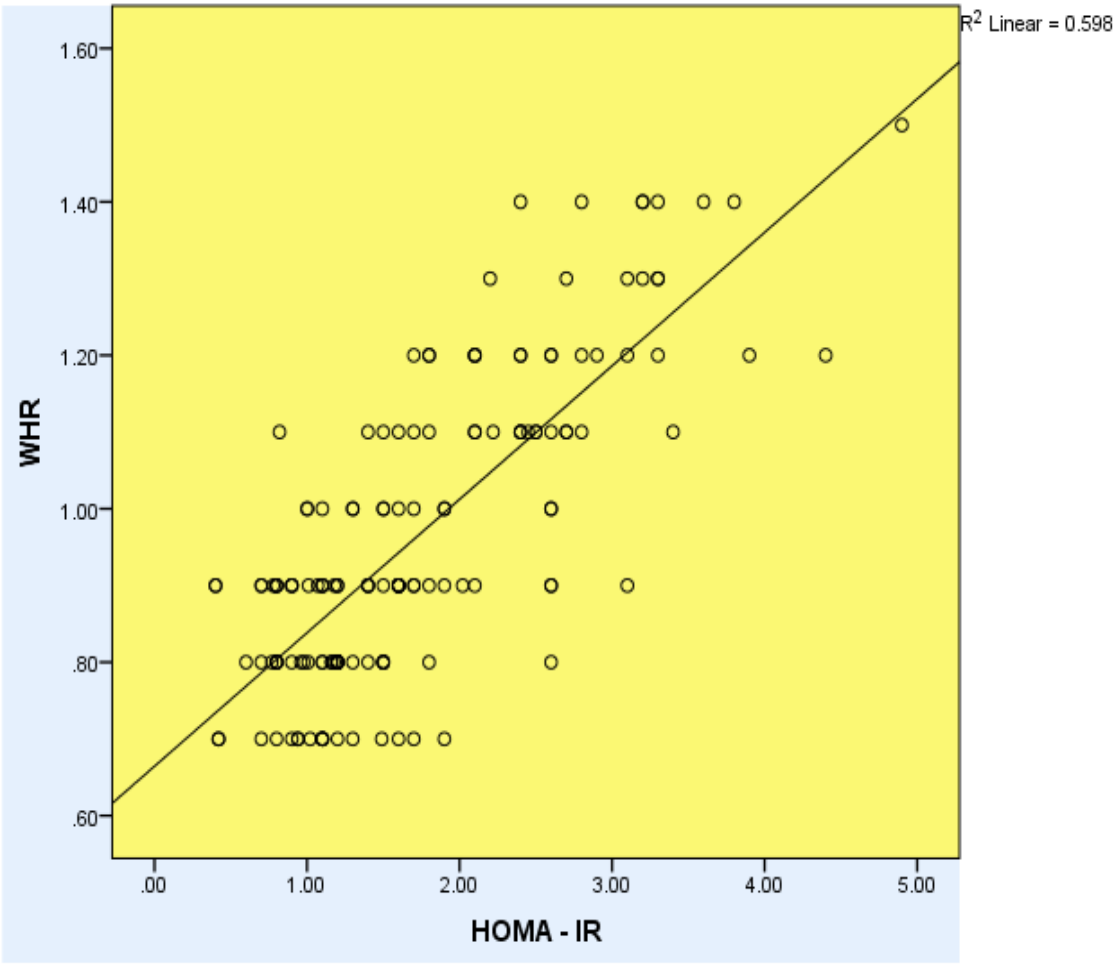
7. WAIST HIP CIRCUMFERENCE RATIO :

Study group	Number of subjects	Body mass index		p Value
		Mean	Standard deviation	
NDP	50	0.86	0.09	**p=0.0001 significant**
SDP	50	0.93	0.14	
BDP	50	1.10	0.23	

Table – 7 showing mean waist hip circumference ratio of offspring of non diabetic parent group (NDP), offspring of single diabetic parent group (SDP) and offspring of both diabetic parent group (BDP) as 0.86, 0.93 and 1.10 respectively.

p Value by using ANOVA is 0.0001 which is statistically significant

8. CORRELATION BETWEEN WAIST HIP RATIO AND HOMA – IR:



8. CORRELATION BETWEEN WAIST HIP CIRCUMFERENCE RATIO AND HOMA – IR:

Parameter	HOMA – IR	
	r – Value	p – Value
Waist hip circumference ratio	0.773	<0.00001

Table 8 shows that, by Pearson correlation, there was a strong positive linear correlation between Waist hip circumference ratio and Insulin resistance with r value of 0.773 and significant p value of < 0.00001.

9. SHEFFE MULTIPLE PAIR WISE COMPARISON OF PHYSICAL AND BIOCHEMICAL PARAMETERS:

Parameters	NDPVS SDP p-value	NDPVS BDP p-value	SDPVS BDP p-value
Body weight kg	0.06	0.006	0.65
BMI	0.5	0.005	0.015
Fasting blood glucose (mmol/l)	0.0004	0.0003	0.0017
Fasting Insulin (μU/ml)	0.0008	0.0002	0.0007
HOMA IR	0.0007	0.0001	0.0006
Waist hip circumference ratio	0.172	0.0009	0.0176

Table 8 shows that Insulin Resistance as assessed by HOMA-IR was statistically significant ($p<0.05$) in NDP versus BDP and SDP versus BDP. There was also a statistical significant difference values of Fasting blood glucose and Fasting insulin levels between NDP versus BDP and SDP versus BDP groups.

DISCUSSION

DISCUSSION

This present study was carried out among offspring of diabetic parents to detect hyperinsulinemia and insulin resistance at an early stage in life which can help to establish measures for preventing the development of type 2 diabetes mellitus, so that lifestyle modifications (dietary habits, exercise and weight loss) are accordingly advised to such individuals.

Anton J. M. Wagenmakers et al The global epidemic of type 2diabetes is a pressing public health concern associated with a rapidly growing socioeconomic burden. Insulin resistance (IR) is an early event in the pathogenesis of type 2 diabetes mellitus. In patients with type 2 diabetes, Insulin resistance is progressive and after several years often leads to the development of symptoms of diabetes mellitus (including hypertriglyceridaemia, obesity and pathology of the macro and microvasculature). Eventually (after more than ten years) severe medical complications may develop, including retinopathy, neuropathy, tissue necrosis in the extremities, renal failure and cardiomyopathy. Therefore these complications can be prevented by detection of insulin resistance even in the late adolescent age and so that lifestyle modifications (dietary habits, exercise and weight loss) and medications are advised accordingly to such individuals.

Warram et al, 1990 reported that on the basis of intravenous glucose tolerance tests among white subjects, insulin resistance is a strong predictor of Non insulin dependent diabetes mellitus in the offspring of parents with Non insulin dependent diabetes mellitus.

Lilliojaet al.1991 proposed that insulin resistance was a strongest predictor of Non insulin dependent diabetes mellitus.

Shahid et al. 2008 found that the offspring of single and both diabetic parents were increased prevalence of certain metabolic risk factors which may trigger or perpetuate the development of diabetes and cardiovascular disorders and also documented that offspring of diabetic parents are associated with increased predicting factors for developing diabetes. The incidence of diabetes mellitus for offspring of non diabetic parent is 10-11%, incidence of diabetes mellitus for offspring of single diabetic parent is 29-30% and incidence of diabetes mellitus for offspring of both diabetic parent is 55-60%.

A progressive reduction over the last few decades of daily engagement in physically demanding activities and growth in unbalanced diets are generally considered to be the primary causes of the dramatic rise in type 2 diabetes mellitus.

In this study we have assessed that offspring of diabetic parents have hyperinsulinemia and raised insulin resistance in early age compared to offspring of non diabetic parents which is a significant predictor for diabetes mellitus. This study includes 150 participants and categorised into three groups which NDP as offspring of non diabetic parents, SDP as offspring of single diabetic parent and BDP as offspring of both diabetic parents. Most confounding factors were excluded and values obtained were analysed and categorised into insulin sensitive, borderline and insulin resistance. In this present study in the NDP group the distribution of number of subjects with borderline insulin resistance were 2, the number of subjects with borderline insulin resistance in SDP group were 12, and in the BDP group the number of subjects with borderline insulin resistance were 23 and 4 subjects have insulin resistance in this group. This shows that insulin resistance is prevalent in BDP group compared to SDP as well as NDP group.

The evolving stage of insulin resistance starts and it is evident biochemically from late adolescent and young adult age group. The mean age group of this study were 18.06, 18.18 and 18.94 for NDP, SDP and BDP groups respectively. This study also shows a significant number of subjects with insulin resistance at an early age of their life.

Fasting blood sugar values were normal in all the three groups as the mean fasting blood glucose values were 75.6, 80.8 and 83.5 in NDP, SDP and BDP groups respectively. Even though when the fasting blood glucose values are within normal limits, it is higher in BDP group compared to SDP and NDP group and there was significant difference in fasting blood glucose levels in between NDP versus BDP and SDP versus BDP, and the p value is <0.05. The high normal rise in blood glucose levels in BDP and SDP group is probably due to significant increase in insulin resistance.

Meraj Rahim **et al, 2014** Hyperinsulinemia governs the predicting factor of type 2 diabetes mellitus in those subjects who gave a history of diabetes. Mean Fasting insulin levels of NDP, SDP and BDP groups were 5.84, 8.02 and 11.8 respectively. Even though when the fasting insulin values are within normal limits, it is higher in BDP group, high normal in SDP group normal in NDP group and there was significant difference in fasting insulin levels in between NDP versus BDP and SDP versus BDP, and the p value is <0.05. This rise in fasting insulin levels in BDP group is due to increase in insulin resistance and there is an increase in blood glucose level, to compensate this rise in blood glucose level there is a compensatory rise in insulin levels. Thus BDP groups have more insulin levels compared to other two groups and this hyperinsulinemia factor governs insulin resistance.

ENZO BONORA et al 2002 proposed that HOMA-IR seems to be a reliable tool in the assessment of insulin resistance, which can be used as a valid alternative to the glucose clamp or other sophisticated techniques in epidemiological settings. Indeed, longitudinal studies of large samples are not feasible with the glucose clamp. Also proved that HOMA-IR method has strong correlation(r=0.87) with euglycemic glucose clamp technique.

Mehmet et al 2004, in a study demonstrates that HOMA-IR has high sensitivity and specificity for measuring insulin resistance

Mean Insulin resistance assessed by homeostatic model of insulin resistance method (HOMA-IR) for NDP, SDP and BDP groups were 1.05, 1.59 and 2.62 respectively. Even though when the insulin resistance values are within normal limits, it is higher in BDP group compared to SDP and NDP group and there was significant difference in insulin resistance levels in between NDP versus BDP and SDP versus BDP, and the p value is <0.05. The high level of insulin resistance in BDP group compared to SDP and NDP group shows that there is a strong genetic predisposition for occurrence of type 2 diabetes mellitus in offspring of both diabetic parents compared to offspring of single diabetic parent. And the offspring of single diabetic parent also has strong genetic predisposition for occurrence of type 2 diabetes mellitus compared to offspring of non diabetic parents.

Meraj Rahim et al, 2014proves that insulin resistance the predicting factor of type 2 diabetes mellitus has strong correlation with body mass index. Mean BMI values for NDP, SDP and BDP groups were 21.66, 22.33 and 23.06 respectively. Eventhough according to selection criteria all groups have normal BMI of less than 25, it is high normal in BDP group compared to SDP and NDP group and there was significant difference in BMI levels in between NDP versus BDP, and the p value is <0.05. There is also a positive correlation between body mass index and insulin resistance levels.

Shobha MV et al 2013in a study, it was assessed that waist hip circumference ratio was one of the predictors of Insulin Resistance, as it denotes central adiposity besides other anthropometric measurement. In this study, the waist hip ratio was more in BDP group compared to other two groups and the insulin resistance was also more in this BDP group compared to SDP and NDP groups. This waist hip ratio strongly correlates with the insulin resistance with r value of 0.77 with significant p value <0.05.

CONCLUSION

CONCLUSION

In this study, it is found that insulin resistance is increased in young adults with both diabetic parents compared to offspring of single diabetic parent and offspring of non diabetic parent groups. This shows that the offspring of diabetic parents has insulin resistance at an early stage of life. So that the lifestyle modifications are accordingly advised to such individuals to postpone the occurrence of onset of type 2 diabetes mellitus and thereby further complications also prevented.

Hence it is recommended to assess the insulin resistance at an early stage of life. It is suggested to do insulin resistance screening in person with diabetic parents as they are in high risk to develop diabetic mellitus.

Screening can be done by Homeostatic model of assessment of insulin resistance (HOMA – IR) method as it is a simpler, cheaper, less labor-intensive, less time consuming and more acceptable to young people.

Understanding the pathogenesis of the disease will help to identify the better targets of treatment. Early screening for insulin resistance and prompt lifestyle modifications will help to delay the onset of diabetes mellitus.

As most of the complications of diabetes mellitus depend on duration of hyperglycemia, early screening to identify insulin resistance and achieving pharmacological targets to reduce insulin resistance, thereby prevents the complication of Diabetes mellitus.

LIMITATIONS:

Further studies can be planned

- With large sample size.
- With the inclusion of grandparents history of diabetes mellitus.
- Inclusion in routine lipid profile
- Inclusion of sibling history of diabetes mellitus.

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BIBLIOGRAPHY

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PROFORMA

STUDY PROFORMA

Name: **Age: years**

Sex: **Occupation :**

Address:

H/o Systemic Illness

H/o Diabetes Mellitus **:**Yes (or) No

H/o Hypertension **:**Yes (or) No.

H/o of Smoking **:** Yes (or) No.

H/o of Alcoholism **:** Yes (or) No.

H/o Endocrine disorder **:** Yes (or) No.

H/o cardiovascular disorders **:** Yes (or) No.

H/o Respiratory disorders **:** Yes (or) No.

H/o Neuromuscular disorder **:** Yes (or) No.

Family history of father having Diabetes Mellitus**:** Yes (or) No

- Duration in years**:**

-Duration of treatment**:**

Family history of Mother having Diabetes Mellitus**:** Yes (or) No

-Duration in years**:**

-Duration of treatment**:**

Diet history **:** Vegetarian / Non vegetarian

Drug history:

H/o taking steroids **:** Yes (or) No

H/o taking hypoglycemic agents **:** Yes (or) No

H/o taking androgens **:** Yes (or) No

General Examination:

Consciousness: Orientation:

Comfortable at rest: Pallor:

Cyanosis: Clubbing:

Jaundice : Lymphadenopathy :

Pedal oedema : Acanthosis nigricans :

Vital signs

Temperature : F

Respiratory rate: /minute

Pulse rate : /minute

Blood Pressure :Systolic: mmHg

Diastolic: mmHg

Anthropometric measurements:

Height : cm

Weight : kg

BMI (kg/m^2) :

Waist circumference : cm

Hip circumference : cm

Waist Hip ratio:

Systemic Examinations:

Cardiovascular System :

Respiratory System:

Abdomen :

Central Nervous System**:**

INVESTIGATIONS:

Fasting blood glucose : mg/dl

Fasting serum insulin : μU/ml

Homeostatic Model Assessment of Insulin Resistance
(HOMA–IR Index): Fasting Insulin (μU/ml) X Fasting Plasma glucose(mg/dl) / 405

மருத்துவப்பரிசோதனை முறைகளை பற்றி மருத்துவரிடம் தெரிந்து கொண்டேன். இதனை மேற்கொள்ளநான் முழுமனதுடன் சம்மதிக்கிறேன்.

MASTER CHART

MASTER CHART

s.no	Name	age	sex	Height cms	Weight kg	BMI Kg/m^2	WHR	Pulse rate min	Respiratory rate min	Fasting blood sugar mg/dl	Fasting insulin mU/ml	HOMA-IR
1	Saranya	18	F	172	57	24.3	1.2	72	18	85	18.3	3.9
2	Manikandan	19	F	160	62	24.6	1.4	82	18	92	16.9	3.8
3	Shyam	20	M	162	59	22.5	1.5	75	20	78	16.3	4.9
4	Vinitha	20	F	167	65	23.6	1.2	74	18	83	17.8	4.4
5	Srikamala	20	F	176	70	24.2	1.3	74	20	77	16.2	3.3
6	Abharajithan	21	M	168	66	23.9	1.1	75	20	89	9.5	3.4
7	Sudharsana	18	F	162	62	24.8	1	78	18	88	11.8	2.6
8	Chandru	19	M	172	65	22.6	0.8	76	18	86	9.8	1.8
9	Suresh	19	M	165	63	23.2	1	71	18	90	11.7	2.6
10	Nandhakishor	18	M	176	74	24.2	1.3	72	20	85	13.2	2.7
11	Saathveega	19	F	168	65	24.3	1.3	65	18	84	14.5	3.3
12	Suvalakshmi	20	F	160	60	21.2	1.1	64	20	82	13.2	2.6
13	ezhilalarasan	18	M	158	60	24.2	1.2	82	18	89	14.1	3.1
14	Swathy	18	F	162	62	24.8	0.7	75	20	76	9.9	1.9
15	Navya	18	F	164	62	23.2	0.9	74	20	79	9.6	1.9
16	Thajesh	18	M	178	72	22.4	1.1	74	18	84	8.2	1.8
17	Reena	18	M	166	50	18.4	0.9	75	18	88	7.5	1.7
18	Varshanthini	20	F	180	68	20.9	1.2	78	18	88	11.6	2.6
19	Jeeva	21	M	165	59	21.6	0.7	76	20	86	7.8	1.6
20	Venkatesh	18	M	170	71	24.5	1	71	18	72	8.9	1.6
21	Shreeram	19	M	158	60	24.1	1.1	72	20	86	11.2	2.7
22	Sheik	19	M	165	56	22.3	1.2	65	18	81	14.2	2.9
23	Vijayalakshmi	18	F	172	57	24.3	1.2	82	20	80	9.7	2.1
24	Yugendran	19	M	180	60	21.2	1.1	75	20	79	10.5	2.1
25	Vikneshvar	20	M	156	58	24.2	1.4	74	18	84	15.23	3.2

s.no	Name	age	sex	Height cms	Weight kg	BMI Kg/m^2	WHR	Pulse rate min	Respiratory rate min	Fasting blood sugar mg/dl	Fasting insulin mU/ml	HOMA-IR
26	Balaji	18	M	166	50	18.2	0.9	82	18	85	12.3	2.6
27	Nithya	18	F	163	58	**21.8**	0.8	75	20	87	12.4	2.6
28	Nithish	18	M	162	62	24.8	0.7	74	20	77	8.9	1.7
29	Pooja	18	F	166	65	23.6	1.1	74	18	87	11.2	2.7
30	Nancy	18	F	176	53	18.2	1.2	75	22	90	14.2	3.3
31	Priyanka	20	M	156	58	24.9	0.9	78	20	71	9.8	2.6
32	Dinesh	20	M	168	61	22.3	0.7	76	18	69	5.3	1.1
33	Elangovan	20	M	162	49	19.2	1.1	71	20	72	7.5	1.4
34	Gowsika	21	F	157	60	19.8	1.3	72	20	73	11.2	2.2
35	Sreehari	18	M	153	55	24.8	0.9	65	18	94	13.5	3.1
36	Gokul	19	F	157	65	22.4	1.1	64	22	75	14.2	2.8
37	Shivani	19	F	154	62	22.5	1	68	20	84	9.6	1.9
38	Rithvika	18	F	168	70	24.2	1.2	74	18	76	11.2	2.1
39	Manohar	19	M	165	63	23.1	1.4	75	20	88	9.9	3.3
40	Sreeranjani	20	F	166	64	23.5	1.3	78	20	82	14.2	3.2
41	Jewel	18	M	176	70	24.2	1.4	76	18	86	15.2	3.2
42	Anitha	18	F	168	66	23.9	1.1	70	22	92	9.7	2.5
43	Anzoom	18	F	164	62	23.2	1.1	75	20	86	11.2	2.4
44	Thasneem	18	F	176	72	24.5	1.3	74	18	84	14.5	3.1
45	Darshan	20	M	169	69	24.9	1.2	74	20	82	12.5	2.8
46	Pandiraj	21	M	164	60	24.2	1.4	75	20	93	16.5	3.6
47	Ramesh	18	M	168	65	23.8	0.8	78	18	85	5.3	1.2
48	Abarna	19	F	165	63	23.2	1.1	76	22	87	11.4	2.45
49	Anjali	19	F	176	74	24.2	1.4	71	20	89	12.5	2.8
50	Sivakumari	18	F	168	65	24.3	0.9	72	18	92	8.9	2.02

s.no	Name	age	sex	Height cms	Weight kg	BMI Kg/m^2	WHR	Respiratory rate min	Fasting blood sugar mg/dl	Fasting insulin mU/ml	HOMA-IR
51	Praveen	18	M	157	61	20.5	0.8	22	80	3.93	0.77
52	Ramprasath	17	M	155	70	22.5	1.1	20	79	4.23	0.82
53	Karthika	18	F	162	71	19.1	0.8	18	72	4.38	0.8
54	Karthik	19	M	166	62	23.3	0.9	20	80	5.78	1.1
55	Kavin	18	M	153	54	18.2	0.9	20	78	4.54	0.9
56	Lavanya	18	F	160	65	19	0.7	18	80	5.82	1.1
57	Vishnu	17	M	153	54	18.1	0.8	18	72	5.1	0.96
58	Aravind	18	M	162	70	22.4	0.9	20	68	2.6	0.4
59	Aishwarya	19	F	166	61	23.6	1.1	20	94	11.1	2.6
60	Raghadarsh	20	F	153	54	23.1	0.9	18	74	4.8	0.8
61	Ajeeth	18	M	153	53	22.8	0.8	22	80	5.2	0.98
62	Sripriya	17	F	157	65	22.6	0.9	20	78	6.2	1.1
63	Vidhya	19	F	155	58	24.2	1.2	18	85	7.3	1.7
64	Nathiya	18	F	162	62	23.1	1.1	20	89	12.1	2.6
65	Gayathri	18	F	166	60	21.4	0.8	20	68	4.3	0.7
66	Nivetha	17	F	177	71	22.6	0.7	18	78	4.38	0.8
67	Bharath	17	M	160	58	22.3	1	22	80	7.89	1.5
68	Joel	18	M	170	62	21.4	0.8	20	84	4.54	0.9
69	Manikandan	19	M	170	68	23.4	0.9	18	75	5.82	1.07
70	Aravinth	17	M	153	50	21.7	0.9	20	71	5.7	0.9
71	Jerlin	18	M	150	53	23.6	0.8	20	72	7.01	1.2
72	Lokesh	17	M	157	55	22	0.9	18	72	8.2	1.4
73	Yogeshwari	18	F	166	50	18.4	0.9	22	68	10.1	1.2
74	Yuvathi	17	F	180	68	20.9	0.7	17	66	2.6	0.42
75	Arthi	17	F	165	59	21.6	0.8	17	74	4.6	0.8

s.no	Name	age	sex	Height cms	Weight kg	BMI Kg/m^2	WHR	Pulse rate min	Respiratory rate min	Fasting blood sugar mg/dl	Fasting insulin mU/ml	HOMA-IR
76	Madhumith	17	F	170	54	22.6	1	75	17	78	5.2	1.001
77	Akilasree	18	F	165	53	19.5	0.7	74	18	80	4.8	0.94
78	Darshini	19	F	154	59	24.2	0.8	74	18	76	6.2	1.16
79	Rithika	19	F	163	57	23.8	0.9	74	20	70	7.3	1.6
80	Ramkumar	18	M	154	48	19.2	0.9	75	19	78	10.2	1.4
81	Suresh	17	M	170	49	18	0.9	78	22	76	4.3	0.7
82	Surjith	18	M	176	53	18.2	0.8	76	20	70	4.38	0.6
83	Vinoth	19	M	156	58	25.2	0.9	71	18	68	5.78	0.9
84	Udhay	17	M	168	61	22.3	0.9	72	20	78	4.54	0.8
85	Prithviraj	18	M	162	49	19.2	0.7	65	20	80	5.82	1.1
86	Neha	17	F	162	62	23.7	0.8	64	18	84	5.7	1.18
87	Meena	18	F	169	57	20.3	0.7	68	22	75	10.1	1.2
88	Pramodh	21	M	172	51	17.6	1	74	20	71	8.2	1.3
89	Rishwin	20	M	163	62	22.6	0.8	75	18	69	7.8	1.2
90	Sundar	18	M	166	60	20.6	0.9	78	20	73	**6.6**	1.18
91	Supriya	19	F	165	56	22.3	0.9	76	20	70	4.12	0.7
92	Sumaya	19	F	172	57	24.3	0.8	70	22	80	5.1	1.007
93	Keerthika	18	F	180	60	21.2	0.9	75	20	74	2.6	0.4
94	Surjith	18	M	156	58	24.2	0.9	74	18	69	4.6	0.78
95	Yuvathi	17	F	180	68	20.9	0.7	74	20	66	2.6	0.42
96	Arthi	17	F	165	59	21.6	0.8	75	20	74	4.6	0.8
97	Akilasree	18	F	165	53	19.5	0.7	78	18	80	4.8	0.94
98	Madhusri	17	F	170	54	22.6	1	76	22	78	5.2	1.001
99	Darshini	19	F	154	59	24.2	0.8	75	18	76	6.2	1.16
100	Rithika	19	F	163	57	23.8	0.9	74	19	70	7.3	1.6

s.no	Name	age	sex	Height cms	Weight kg	BMI Kg/m^2	WHR	Pulse rate min	Respiratory rate min	Fasting blood sugar mg/dl	Fasting insulin mU/ml	HOMA-IR
101	Ilakkiya	17	F	163	58	21.8	0.8	75	22	81	7.2	1.5
102	Priyadarshini	17	F	170	71	24.5	0.7	74	20	74	6.61	1.3
103	Jayalakshmi	18	F	158	60	24	1.1	74	18	73	10.2	1.7
104	Jerlin	17	M	166	51	18.5	1	75	20	80	5.31	1.1
105	Ramesh	19	M	169	62	21.7	1.1	78	20	82	12.1	2.4
106	Joel Francis	18	M	168	55	19.5	1.2	76	18	83	8.6	1.8
107	Keerthana K	18	F	172	63	21.3	1.2	71	22	81	8.82	1.8
108	Karthick	17	M	170	60	20.7	0.9	72	20	84	9.7	2.1
109	Kishore	18	M	165	59	21.6	0.8	65	18	74	8.3	1.5
110	Vivek	19	M	166	50	18.2	0.9	64	20	78	9.1	1.8
111	Yogesh	18	M	163	58	21.18	1.1	68	20	**95**	**11.2**	**2.6**
112	Lakshmipriya	18	F	162	55	21.3	0.8	74	22	82	6.3	1.2
113	Vaishnavi	17	F	166	65	23.6	1.2	75	20	89	12.1	2.6
114	Kowshika	17	F	178	71	22.3	1	78	18	76	8.2	1.5
115	Krishnan S	18	M	168	70	24.2	1.1	76	20	82	7.6	1.5
116	Yamuna	19	F	165	63	23.1	0.8	70	20	87	7.2	1.5
117	Lavlin	17	F	166	64	23.5	1	75	18	74	7.4	1.3
118	Nirlin	21	M	176	70	24.2	1	75	22	70	10.2	1.7
119	Madhumitha	17	F	168	66	23.9	0.9	74	20	68	9.6	1.6
120	Vaitheesh	18	F	164	62	23.2	0.7	74	18	72	6.5	1.1
121	Manoj	17	M	178	72	22.4	0.8	75	20	74	4.2	0.8
122	Manikandan	17	M	166	50	18.4	0.7	78	20	86	3.5	0.7
123	Abarna	18	F	180	68	20.9	1.1	68	18	94	11.3	2.6
124	Akila	20	M	165	59	21.6	0.9	70	19	88	6.7	1.4
125	Ahamed	19	M	165	53	19.5	0.8	68	19	78	6.3	1.2

s.no	Name	age	sex	Height cms	Weight kg	BMI Kg/m^2	WHR	Pulse rate min	Respiratory rate min	Fasting blood sugar mg/dl	Fasting insulin mU/ml	HOMA-IR
126	Muthu	18	M	169	69	24.2	0.8	75	20	74	7.6	1.3
127	Nathiya	18	F	169	63	22.3	1.4	74	22	93	12.1	2.6
128	Namanapriy	17	F	176	72	24.5	0.9	74	20	78	8.5	1.6
129	Nivetha B	20	F	169	69	24.9	0.7	75	18	82	4.5	0.9
130	Syed	18	M	164	50	21.6	0.9	78	20	80	5.6	1.1
131	Akilesh	19	M	168	65	23.8	0.8	76	20	74	7.9	1.4
132	Vignesh	17	M	174	69	22.8	0.9	71	18	78	5.6	1.01
133	Partha	18	M	165	51	21.9	0.9	72	22	78	7.8	1.5
134	Navya	19	M	169	63	22.3	0.8	65	20	88	5.6	1.2
135	Neha	19	F	167	65	23.6	0.8	64	18	86	5.4	1.1
136	Avilin	18	M	175	56	18.6	1.2	68	20	90	12.7	2.7
137	Nislin	18	F	172	65	22.6	1	74	20	87	8.9	1.9
138	Rihana	17	F	165	63	23.2	0.9	75	22	74	8.5	1.6
139	Nivetha B	20	F	176	74	24.2	0.7	78	20	70	8.2	1.49
140	Pruthvi Raj	18	M	168	65	24.3	0.9	76	18	68	7.6	1.2
141	Parkavi V	19	F	160	60	21.2	1.1	70	20	92	10.7	2.4
142	Vishnu	19	M	158	60	24.2	1.2	75	20	97	11.1	2.7
143	Parvathy.	18	F	162	62	24.8	0.8	74	18	86	7.2	1.5
144	Abishek	17	M	165	50	18.6	0.9	74	22	82	7.9	1.6
145	Praveen	18	M	163	63	24.9	0.8	75	20	80	5.6	1.1
146	Vidhya	19	F	159	56	24.2	0.9	78	18	78	8.9	1.7
147	Ponnar	20	M	158	53	21.4	0.7	76	20	74	5.6	1.02
148	Naresh	18	M	162	59	22.5	0.9	71	20	76	4.6	0.8
149	Pradhu	19	M	158	51	20.5	0.8	72	20	78	6.5	1.2
150	Prasanna	19	M	160	62	24.6	1.2	75	18	92	12.2	2.6

ABBREVIATION

ABBREVIATION

Sl.No.	ABBREVIATION	EXPANSION
1.	DM	Diabetes Mellitus
2.	NIDDM	Non insulin dependent diabetes mellitus
3.	HOMA - IR	Homeostatic model assessment of insulin resistance
4.	NDP	Non Diabetic Parent
5.	SDP	Single Diabetic Parent
6.	BDP	Both Diabetic Parent
7.	IR	Insulin resistance
8.	TGL	Triglyceride
9.	DKA	Diabetic keto acidosis
10.	FBS	Fasting blood sugar
11.	WHR	Waist hip circumference ratio

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MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University,
Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.S.Kannan
Course	:	PG in MD., Physiology
Period of Study	:	2016-2019
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Assessment of insulin resistance in offspring of diabetic and Non diabetic parents
Ethical Committee as on	:	13.04.18

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

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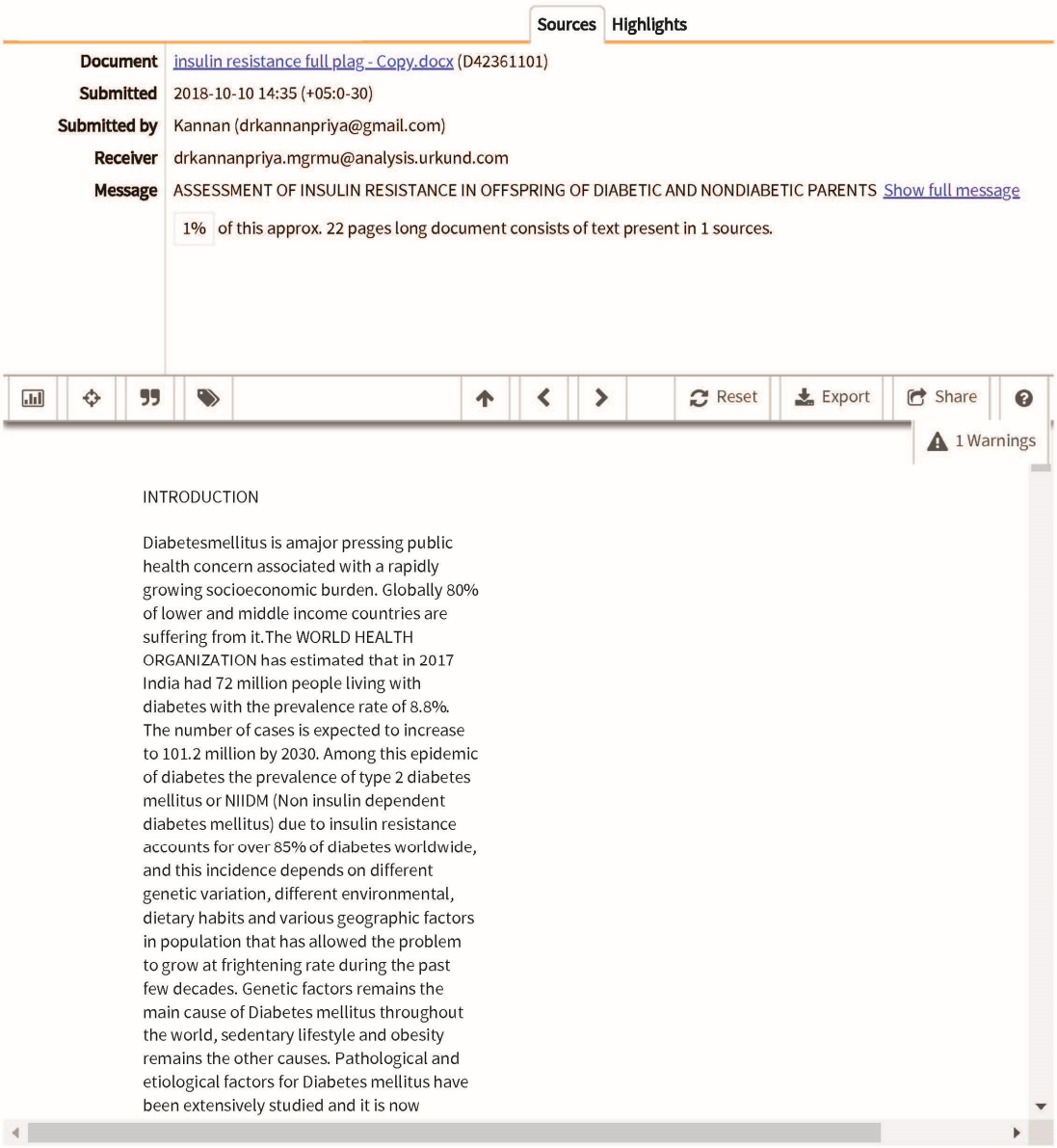
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INTRODUCTION
Diabetesmellitus is amajor pressing public health concern associated with a rapidly growing socioeconomic burden. Globally 80% of lower and middle income countries are suffering from it.The WORLD HEALTH ORGANIZATION has estimated that in 2017 India had 72 million people living with diabetes with the prevalence rate of 8.8%. The number of cases is expected to increase to 101.2 million by 2030. Among this epidemic of diabetes the prevalence of type 2 diabetes mellitus or NIIDM (Non insulin dependent diabetes mellitus) due to insulin resistance accounts for over 85% of diabetes worldwide, and this incidence depends on different genetic variation, different environmental, dietary habits and various geographic factors in population that has allowed the problem to grow at frightening rate during the past few decades. Genetic factors remains the main cause of Diabetes mellitus throughout the world, sedentary lifestyle and obesity remains the other causes. Pathological and etiological factors for Diabetes mellitus have been extensively studied and it is now

CERTIFICATE

This is to certify that this dissertation titled **"ASSESSMENT OF INSULIN RESISTANCE IN OFFSPRING OF DIABETIC AND NON DIABETIC PARENTS"** of the candidate **Dr.S.KANNAN** for the award of **M.D** degree in the branch of PHYSIOLOGY. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file containing from introduction to conclusion pages and result shows **0** percentage of plagiarism in the dissertation.

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Institute of Physiology,

Madurai Medical College,

Madurai.